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Annales d'Endocrinologie

Volume 78, Issue 1,
Pages 1-74
(February 2017)

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Annales
d’Endocrinologie
Annals of Endocrinology

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Cover photo: “Flip-flop phenomen” of thyroid cancer cells at the origin of the complementarity of 18F-FDG-PET and post-therapeutic Iodine 131 scan. a. Patient presenting with bone metastases in the right temporal bone and right humeral head demonstrating intense Iodine 131 uptake (1.a.1) but no 18F-FDG avidity (1.a.2). b. Patient presenting with cervical and upper mediastinal lymph nodes and lung metastases demonstrating no Iodine 131 uptake (1.b.1) but an intense 18F-FDG uptake (1.b.2).
Photo de couverture : Effet “Flip-Flop” des cellules de cancers thyroïdiens à l’origine de la complémentarité de la TEP-18F-FDG et de la scintigraphie après administration thérapeutique d’Iode 131. a. Patient présentant des métastases osseuses de l’os temporal droit et de la tête humérale droite avec intense fixation de l’Iode 131 (1.a.1) mais absence totale d’avidité pour le 18-FDG (1.a.2). b. Patient avec adénopathies cervico-médiastinales et métastases pulmonaires montrant l’absence de fixation de l’Iode 131 (1.b.1) mais une intense fixation du 18F-FDG (1.b.2).

Annales d’Endocrinologie (ISSN 0003-4266) 2017 (volume 78) Un an ; 6 numéros. Tarif institutionnel France (TTC) : 518 euros. Voir tarifs complets sur le site www.elsevier-masson.fr/revue/180
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Responsable de production éditoriale – Charlotte Muczinski. E-mail : c.muczinski@elsevier.com
Publicité – Jean-Marie Pinson. Tél. : +33 (0) 1 71 16 53 10. E-mail : j.pinson@elsevier.com
Partenariats – Noëlle Croisat. Tél. : +33 (0)1 71 16 51 10. E-mail : n.croisat@elsevier.com
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Imprimé en France par Jouve, 53101 Mayenne. Dépôt légal à parution
ISSN : 0003-4266

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Annales d'Endocrinologie
Annals of Endocrinology

Annales d'Endocrinologie 78 (2017) 1–8

Original article

Relative contribution of muscle and liver insulin resistance to dysglycemia in postmenopausal overweight and obese women: A MONET group study

Contribution relative de l'insulinorésistance musculaire et hépatique aux troubles de la régulation glycémique chez des femmes non diabétiques ménopausées obèses ou en surpoids : une étude du groupe Monet

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Abstract

Objectives. – The relative contribution of muscle and liver insulin resistance (IR) in the development of dysglycemia and metabolic abnormalities is difficult to establish. The present study aimed to investigate the relative contribution of muscle IR vs. liver IR to dysglycemia in non-diabetic overweight or obese postmenopausal women and to determine differences in body composition and cardiometabolic indicators associated with hepatic or muscle IR. *Material and methods.* – Secondary analysis of 156 non-diabetic overweight or obese postmenopausal women. Glucose tolerance was measured using an oral glucose tolerance test. Whole-body insulin sensitivity (IS) was determined as glucose disposal rate during a euglycemic-hyperinsulinemic clamp. Muscle and liver IR have been calculated using Abdul-Ghani et al. OGTT-derived formulas. Participant's body compositions as well as cardiometabolic risk indicators were also determined. *Results.* – Overall, 57 (36.5%) of patients had dysglycemia, among them 25 (16.0%); 21 (13.5%); 11 (7.1%) had impaired fasting glycemia, impaired glucose tolerance and combined glucose intolerance respectively. Fifty-three (34.0%) participants were classified as combined IS while on the opposite 51 participants (32.7%) were classified as combined IR and 26 (16.7%) participants had either muscle IR or liver IR. For similar body mass index and total fat mass, participants with liver IR were more likely to have lower whole-body IS, dysglycemia and higher visceral fat, liver fat index, triglycerides and alanine aminotransferase than participants with muscle IR. *Conclusion.* – In the present study, the presence of liver IR is associated with a higher prevalence of dysglycemia, ectopic fat accumulation and metabolic abnormalities than muscle IR.
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Keywords: Obesity; Muscle insulin resistance; Liver insulin resistance; Glucose homeostasis

Résumé

But/objectif. – La contribution relative de la résistance à l'insuline (IR) musculaire (M) et hépatique (H) dans le développement des troubles de la régulation glycémique est difficile à établir. L'objectif de ce travail était d'étudier l'impact de l'IR M vs l'IR H sur les anomalies glycémiques dans

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http://dx.doi.org/10.1016/j.ando.2016.10.003
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une cohorte de patientes non diabétiques ménopausées obèses ou en surpoids et de déterminer les éventuelles différences de composition corporelle et de biomarqueurs cardiométaboliques associés à l'IR M ou H. *Matériels et méthodes.* – Cent cinquante-six femmes non diabétiques ménopausées obèses ou en surpoids ont été étudiées dans une analyse secondaire. La tolérance au glucose a été mesurée au cours d'une hyperglycémie provoquée par voie orale (HGPO). La sensibilité à l'insuline (SI) a été mesurée par une épreuve de clamp hyperinsulinémique euglycémique. L'IR M et l'IR H ont été calculées en utilisant les formules dérivées de l'HGPO décrites par Abdul-Ghani et al. La composition corporelle et des biomarqueurs de risque cardiométabolique ont également été déterminés. *Résultats.* – Globalement, 36,5 % (57) des participantes avaient une dysglycémie dont 25 (16,0 %) avaient une hyperglycémie modérée à jeun non diabétique, 21 (13,5 %) une intolérance au glucose et 11 (7,1 %) une anomalie combinée. Cinquante-trois (34,0 %) participantes étaient classées comme IS M et H tandis que 51 (32,7 %) avaient une IR combinée M et H, 26 (16,7 %) une IR M et 26 (16,7 %) une IR H. Enfin, pour un même indice de masse corporelle et une masse grasse totale comparables, les participantes avec une IR H étaient plus susceptibles d'avoir une IS globale réduite, une dysglycémie, un taux de graisse viscérale plus élevé, des triglycérides et des enzymes hépatiques plus élevés que celles avec IR M. *Conclusion.* – Cette étude démontre que l'IR H est associée à une plus forte prévalence de dysglycémie, d'accumulation de graisse ectopique et d'anomalies métaboliques que l'IR M.

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Mots clés : Obésité ; Insulinorésistance musculaire ; Insulinorésistance hépatique ; Homéostasie du glucose

1. Introduction

Insulin resistance (IR) is defined by impaired response of a target tissue such as adipose tissue, liver and muscle to insulin [1]. Obesity predisposes to IR, which represents a core pathophysiological defect associated with an increase cardiometabolic risk including the development of type 2 diabetes [2]. However, due to the variety of tissues targeted by insulin action, the relative contribution of each insulin-responsive organ in the development of whole-body IR is difficult to establish [3]. In addition, the nature of the tissue (muscle or liver) more affected by IR might be determinant in the expression of the dysglycemia with predominantly fasting or postprandial hyperglycemia. According to previous report, muscle IR was related to postprandial hyperglycaemia while liver IR was rather associated to impaired suppression of hepatic glucose production by insulin resulting into fasting hyperglycaemia [4]. However, Abdul-Ghani et al. found in a sample of non-diabetic Mexican-American participants that those having muscle IR demonstrated both elevated fasting and postprandial glucose levels [5]. Knowing which organ is predominantly affected by IR could allow to investigate if some therapeutic interventions are more efficient in some patients e.g. Metformin in patients with predominant liver IR.

In the present study, we aimed to investigate the relative contribution of muscle IR vs. liver IR to dysglycemia in non-diabetic overweight and obese postmenopausal women. We will also determine if participants with muscle IR present differences in body composition and cardiometabolic risk factors when compared to those with liver IR.

2. Methods

2.1. Participants

For the present *secondary* cross-sectional analysis, the cohort examined was pooled baseline data from two lifestyle intervention studies in comparable populations. Participants to the two studies: *the Montreal-Ottawa New Emerging Team (MONET) Study* ($N = 137$) [6] and *the Complications Associated with Obesity (CAO) Study* ($N = 59$) [7] were non-diabetic overweight or obese postmenopausal women. The studies were approved by the University of Montreal ethics committee. Recruitment procedure and inclusion criteria have been previously described [6,7]. Briefly, women were included in the studies if they were postmenopausal (cessation of menstruation for more than 1 year and a follicle-stimulating hormone level ≥ 30 U/L and no hormone replacement therapy), with a body mass index of 27 kg/m^2 or more (30–40 kg/m^2 for the CAO study) and apparently healthy with no disease requiring immediate medical intervention. Moreover, no participants were taking medication, which could affect glucose homeostasis. Among the 196 subjects recruited in the two studies, 156 subjects had a complete set of baseline data for both the oral glucose tolerance test (OGTT) and the euglycemic hyperinsulinemic clamp. They were thus included in the present secondary analysis.

2.2. Body composition and body fat distribution

As previously described [8], body weight, lean body mass (LBM) and fat mass (FM) were measured using dual-energy X-ray absorptiometry (General Electric Lunar Corporation version 6.10.019, Madison, WI). Body mass index (BMI) was calculated as follow: BMI (kg/m^2) = [body weight/height^2]. Waist circumference (WC) was measured with a non-extendable linear tape measure at the mid-distance between the lowest rib and the iliac crest [9]. A GE High Speed Advantage CT-scanner (General Electric Medical Systems, Milwaukee, WI, USA) was used to measure visceral fat (VAT) area.

2.3. Biochemical measurements

After an overnight fast (12 hours), venous blood samples were collected. Fasting total cholesterol, high-density lipoproteins cholesterol (HDL-C), triglycerides (TG), apoliprotein-B (ApoB), liver enzymes and high-sensitivity c-reactive protein (hs-CRP) were measured as previously described [10–12].

2.4. *Hyperinsulinemic-euglycemic clamp*

Whole-body insulin sensitivity (IS) was measured using the *hyperinsulinemic-euglycemic* clamp technique following the procedure described by De Fronzo et al. (1979) [13]. The test began after a 12-hours overnight fasting. Details on the technique and measurement have been previously described [6,14]. Three basal blood samples were taken over 40 min, after which insulin was infused at a prime constant rate of 75 $mU.m^{-2}.min^{-1}$ for 180 min. Plasma glucose was measured every 5–10 min with a glucose analyzer and maintained at the fasting level with variable infusion rates of 20% dextrose. Insulin sensitivity was determined as glucose infusion rate (GIR) during the last 30 min of the clamp at the steady state and expressed as milligrams per minute per kilogram of LBM (mg/min/kg of LBM).

2.5. *Oral glucose tolerance test*

A 2-hour 75-g OGTT was performed after 12-hours of fasting according to the guidelines of the American Diabetes Association [15]. Blood samples were collected through a venous catheter from an antecubital vein in vacutainer tubes containing EDTA (SST Gel et Clot Activator) at 0, 30, 60, 90 and 120 min. Plasma glucose was rapidly measured on the COBAS INTEGRA 400+ (Roche Diagnostic, Montreal, Canada). Radioimmunoassay kits were used to quantify, in duplicate, insulin plasma levels.

Participants were classified according to their plasma glucose values at 2 h of the OGTT, as having normal glucose tolerance (NGT; < 7.8 mmol/L), impaired glucose tolerance (IGT; ≥ 7.8 mmol/L, and ≤ 11.0 mmol/L). Impaired fasting glucose (IFG) was defined at plasma glucose (IFG; ≥ 6.1, and ≤ 6.9 mmol/L) using basal fasting sample before the OGTT. Those with both IFG and IGT were classified in the group of combined glucose intolerance (CGI). Classifications were done according to the Canadian Diabetes Association guidelines [16].

Using OGTT data, muscle IR index was estimated using Abdul-Ghani et al. formula [17]: Muscle IR = (dG/dt)/mean plasma insulin levels, where dG/dt is the rate of decline in plasma glucose levels and is calculated as the slope of the least square fit to the decline in plasma glucose levels from peak to nadir. Liver IR was estimated according to the formula of Abdul-Ghani et al. formula [17]: Liver IR = glucose (0–30) [AUC] × insulin (0–30) [AUC]), where AUC is the area under the curve during the OGTT.

2.6. *Insulin secretion assessment*

The first phase insulin secretion was determined with Stumvoll's early insulin secretion index [18]: $1.283 + 1.829 \times Ins30$ (pmol/L) $- 138.7 \times Glyc30$ (mmol/L) $+ 3.772 \times Ins0$ (pmol/L). Using this index and the GIR we determined the disposition index which reflects the capacity of ß-cells to compensate for IR.

2.7. *Insulin resistance groups*

Participants were divided according to the present study population median values of Abdul-Ghani et al. [17] muscle and liver IR indices respectively. Participants in the upper median for muscle IR index but in the lower median for liver IR index were considered to be muscle IR and hepatic insulin sensitive (muscle IR group). Conversely, participants in lower median for muscle IR index but in the upper median for liver IR index were considered to have liver IR and muscle IS (liver IR group). Group of combined IR were in the upper median,while participants with combined IS were in the lower median for both muscle and liver IR index.

2.8. *Adiposity indices*

Visceral adiposity index (VAI), was calculated using the formula suggested by Amato et al. [19] The fatty liver index (FLI) was calculated as proposed by Bedogni et al. [20] The lipid accumulation product (LAP) was defined as: LAP = (WC (cm) − 81) × (TG concentration (mmol/L)) [21].

2.9. *Statistical analyses*

The data are expressed as mean ± SD. A one-way ANOVA test was used for means comparison of OGTT glucose and insulin as well as cardiometabolic risk indicators values across groups. For significant different a Scheffé post-hoc test has been used. Chi-square test was used to determine difference between groups according to glucose tolerance status (NGT, IFG, IGT and CGI). Statistical analysis was performed using SPSS Version 17.0 for Windows (Chicago, IL, USA). Statistical significance was set at $P < 0.05$.

3. Results

In our sample of 156 postmenopausal women, 53 (34.0%) participants were classified as combined IS while on the opposite 51 participants (32.7%) were classified as combined IR. Finally 26 (16.7%) participants had either muscle IR or liver IR. All these four groups presented similar weight, BMI, WC and total FM (Table 1). However, muscle IR group had similar VAT values than combined IS group but significantly lower than liver IR group or combined IR group. Similar trend was found for LBM.

A total of 57 (36.5%) of patients had dysglycemia, among them 25 (16.0%); 21 (13.5%); 11 (7.1%) had IFG, IGT and CGI respectively. We examined the relative contribution of muscle and liver IR to dysglycemia by comparing subjects with either combined IS, muscle IR, liver IR or combined IR. As shown in Fig. 1, participants with liver or combined IR were more likely to display dysglycemia when compared to those with muscle IR or combined IS (41.2% and 69.2% vs. 19.2 and 23.1%). Close to 50% of individuals with liver IR and dysglycemia displayed IFG. Moreover, 80% of those with muscle IR and dysglycemia had IGT. The higher prevalence of CGI (15.4%) was found among individuals with combined IR. In this group, 30.8 and 23.1% of individuals had IFG and IGT respectively. Fig. 2 shows plasma glucose excursion during the OGTT for each group of IS/IR. For fasting values and for each time point, individuals with muscle IR showed similar glucose levels when compared to participants with combined IS. On the other hand, fasting glucose values as

Table 1
Body composition, glucose homeostasis and metabolic characteristics of the postmenopausal women ($N = 156$) based on type of insulin sensitivity and insulin resistance.

	Muscle IS and liver IS ($N = 53$)	Muscle IR and liver IS ($N = 26$)	Liver IR and muscle IS ($N = 26$)	Liver IR and muscle IR ($N = 51$)	P-value
Weight (kg)	82.1 ± 13.0	83.6 ± 13.9	87.6 ± 11.1	87.2 ± 14.8	0.174
BMI (kg/m^2)	31.9 ± 4.1	32.6 ± 5.2	33.5 ± 3.4	33.4 ± 3.4	0.218
Waist circumference (cm)	101.7 ± 11.4	101.8 ± 11.1	104.8 ± 9.3	106.5 ± 10.2	0.089
LBM (kg)	41.8 ± 5.4^{a}	40.7 ± 4.9^{a}	44.6 ± 5.3^{b}	43.9 ± 6.7^{b}	0.026
Fat mass (kg)	37.9 ± 9	40.6 ± 10.8	40.7 ± 7.0	41.0 ± 9.3	0.325
VAT (cm^2)	168.2 ± 44.9^{a}	176.9 ± 51.8^{a}	190.5 ± 56.3^{b}	209.3 ± 51.6^{b}	0.001
Fasting glucose (mmol/L)	5.2 ± 0.4^{a}	5.2 ± 0.6^{a}	5.4 ± 0.5^{a,b}	5.5 ± 0.6^{b}	0.017
2 h OGTT glucose (mmol/L)	5.8 ± 1.4^{a}	6.2 ± 1.5^{b}	7.3 ± 1.7^{c}	6.7 ± 1.9^{c,b}	0.001
Fasting insulin (μUI/mL)	12.0 ± 1.4^{a}	14.1 ± 4.7^{a}	16.3 ± 4.2^{b}	20.7 ± 1.9^{c}	< 0.001
2 h OGTT insulin (μUI/mL)	50.9 ± 25.8^{a}	75.9 ± 26.2^{a,b}	88.6 ± 42.3^{b}	132.7 ± 92.5^{b}	< 0.001
Triglycerides (mmol/L)	1.4 ± 0.5^{a}	1.5 ± 0.5^{a},^{b}	1.6 ± 0.8^{a,b}	1.9 ± 0.8^{b}	0.006
HDL-C (mmol/L)	1.5 ± 0.3	1.6 ± 0.4	1.4 ± 0.3	1.4 ± 0.3	0.130
Total cholesterol (mmol/L)	5.3 ± 0.9	5.5 ± 0.9	5.3 ± 0.8	5.4 ± 0.9	0.709
ApoB (g/L)	1.0 ± 0.2	1.0 ± 0.2	1.0 ± 0.2	1.0 ± 0.3	0.384
Systolic blood pressure (mmHg)	121 ± 15	122 ± 13	120 ± 12	125 ± 15	0.461
Diastolic blood pressure (mmHg)	76 ± 8	76 ± 6	77 ± 7	78 ± 9	0.714
hsCRP (g/L)	2.3 ± 1.8^{a}	3.2 ± 2.4^{a,b}	3.4 ± 2.7^{a,b}	4.2 ± 2.2^{b}	0.001
AST (IU/L)	19.0 ± 5.6^{a}	20.4 ± 5.3^{a}	20.2 ± 5.7^{a}	23.7 ± 7.8^{b}	0.003
ALT (IU/L)	19.9 ± 9.9^{a}	28.0 ± 12.6^{b}	34.3 ± 7.7^{c}	31.7 ± 18.4^{c}	< 0.001
GGT (IU/L)	22.3 ± 23.8	26.5 ± 14.6	25.8 ± 12.4	36.5 ± 36.8	0.047
VAI	1.9 ± 0.9^{a}	2.0 ± 0.9^{a}	2.4 ± 1.5^{a,b}	2.8 ± 1.6^{b}	0.001
LAP	58.0 ± 22.5^{a}	66.7 ± 27.6^{b}	77.8 ± 44.1^{b}	89.0 ± 41.0^{b}	< 0.001
FLI	61.4 ± 19.4^{a}	69.3 ± 18.7^{b}	74.8 ± 17.8^{b}	79.0 ± 17.6^{b}	< 0.001
HOMA-IR	2.7 ± 0.7^{a}	3.0 ± 0.9^{a}	3.8 ± 1.2^{b}	4.5 ± 2.0^{b}	< 0.001
Glucose disposal rate (mg/min/kg of LBM)	13.5 ± 3.1^{a}	12.6 ± 2.2^{a}	10.6 ± 2.8^{b}	10.2 ± 2.8^{b}	< 0.001

IS: insulin sensitive, IR: insulin resistant, BMI: body mass index, LBM: lean body mass, VAT: visceral fat, OGTT: oral glucose tolerance test, HDL-C: high-density lipoprotein cholesterol, ApoB: apolipoprotein B, HsCRP: high sensitive C-reactive protein, AST: aspartate aminotransferase, ALT: alanine aminotransferase, GGT: gamma-glutamyl transpeptidase, VAI: visceral adiposity index, LAP: lipid accumulation product, FLI: fatty liver index, LBM: lean body mass. No significant difference between the groups for the variables having the same letters on the same row of the table. Significant difference from $P < 0.05$ to $P < 0.001$.

well as postprandial values were alike between participants with liver IR and combined IR. Muscle IR group presented lower plasma glucose values during OGTT than liver IR group, however these differences were not statistically significant. Insulin secretion during each of the OGTT time point was significantly higher in the combined IR group than the other groups of IR/IS (Fig. 3). No significant difference for plasma insulin values was found between muscle IR and liver IR group at baseline and during OGTT.

In Fig. 4, we present the distribution of IS/IR groups according to tertiles of insulin sensitivity values as measured by the clamp. According to the results, 59.6% of participants with combined IS were in the higher tertile of IS compared to 42.3, 11.5 and 13.7% of participants with muscle IR, liver IR and combined

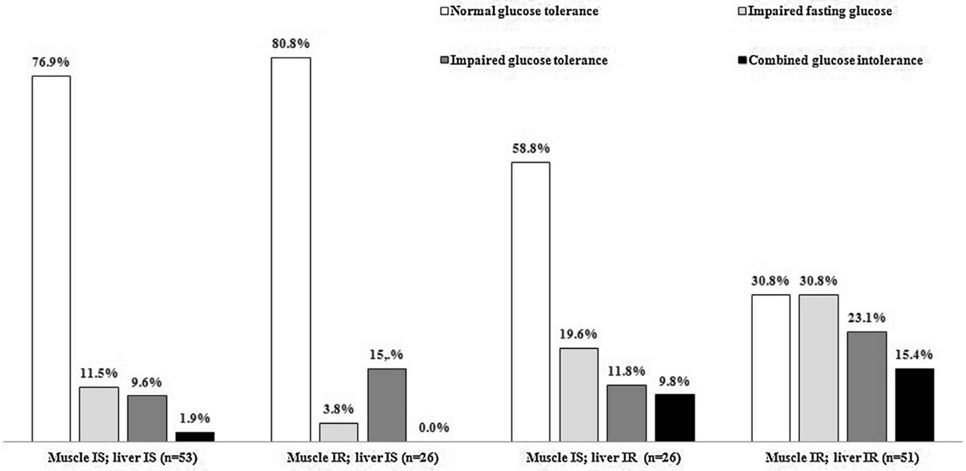

Fig. 1. Glucose tolerance status of postmenopausal women ($N = 156$) according to the type of insulin sensitivity and insulin resistance; P-value $\chi^2 = 0.004$. IS: insulin sensitive, IR: insulin resistant.

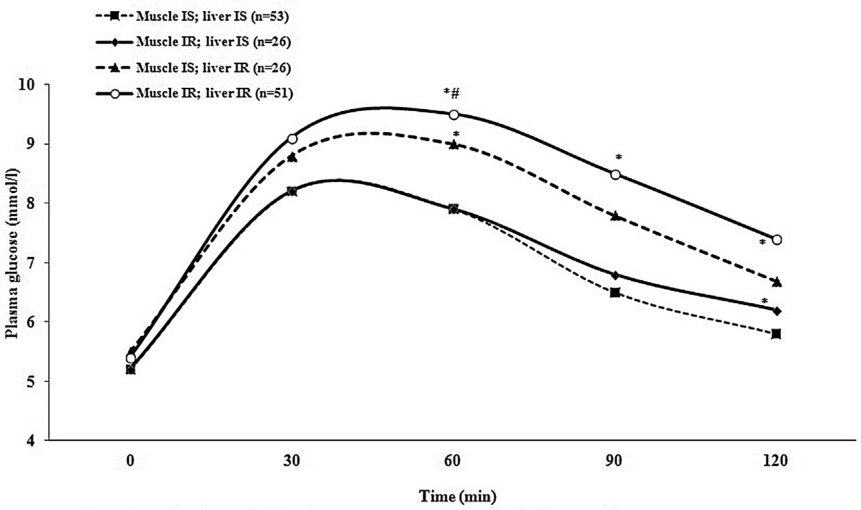

Fig. 2. Plasma glucose levels during the OGTT test of the postmenopausal women ($N = 156$) according to the type of insulin sensitivity and insulin resistance. *: $P < 0.05$ versus muscle IS; liver IS; #: $P < 0.05$ versus muscle IR; liver IS; IS: insulin sensitive, IR: insulin resistant.

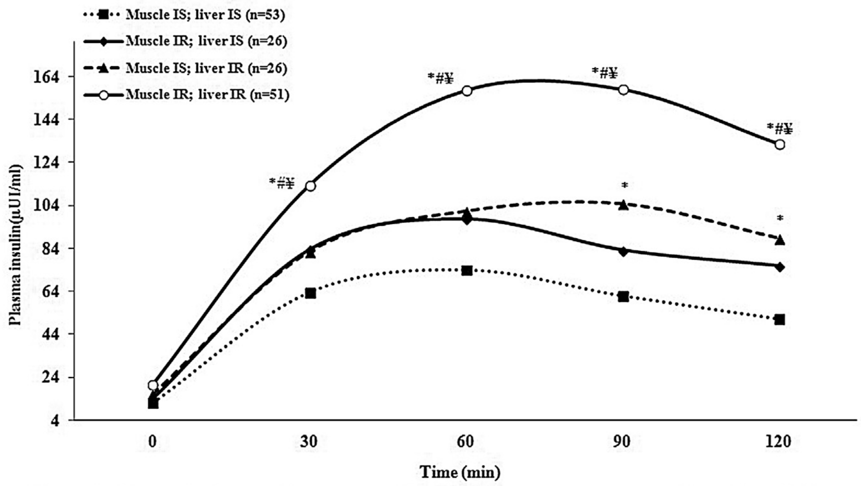

Fig. 3. Plasma insulin levels during the OGTT test of the postmenopausal women ($N = 156$) according to the type of insulin sensitivity and insulin resistance. *: $P < 0.05$ versus muscle IS; liver IS; #: $P < 0.05$ versus muscle IR; liver IS; ¥: $P < 0.05$ versus muscle IS; liver IR; IS: insulin sensitive, IR: insulin resistant.

IR respectively. In addition, 50% of participants with liver IR were in the lower tertile of IS compared to 11.5% in the muscle IR group.

Fig. 5 presents the disposition index: early insulin secretion during the OGTT adjusted for insulin sensitivity as determined by the clamp among each group of IR/IS. Results showed an increased insulin secretion and reduced IS in the presence of IR.

The cardiometabolic risk indicators for each group of IS/IR are shown in Table 1. When considering lipid profile biomarkers, no significant difference was found between groups for total cholesterol, HDL-C, and ApoB. However, TG values were significantly higher in liver IR or combined IR groups than muscle IR or combined IS groups. As an inflammatory status marker, hsCRP values were significantly higher in the combined IR group than the combined IS group but not significantly different than muscle IR and liver IR groups. Similar trends were found for FLI and LAP indices. Liver enzymes were increased in presence of liver IR. For example, ALT values were significantly higher in liver IR than muscle IR and combined IS groups.

4. Discussion

4.1. Insulin resistance and dysglycemia

In the present study, as expected, we found that IFG was the glucose abnormality phenotype most related to liver IR while muscle IR was often associated with IGT phenotype. Furthermore, CGI prevalence was higher among subjects with combined IR. These results are in line with previous investigations [4,22]. However, not all participants with IR have glucose abnormalities. Individuals with muscle IR had significantly less dysglycemia and more efficient IR compensation by insulin secretion than those with liver IR. Abdul-Ghani et al. [5] have previously found that subjects with muscle IR had a greater fasting and 2-h plasma glucose concentration during the OGTT than those with liver IR but they did not determine IR compensation by insulin secretion in the two groups. It should be also emphasized that we performed the hyperinsulinemic-euglycemic clamp technique using relatively

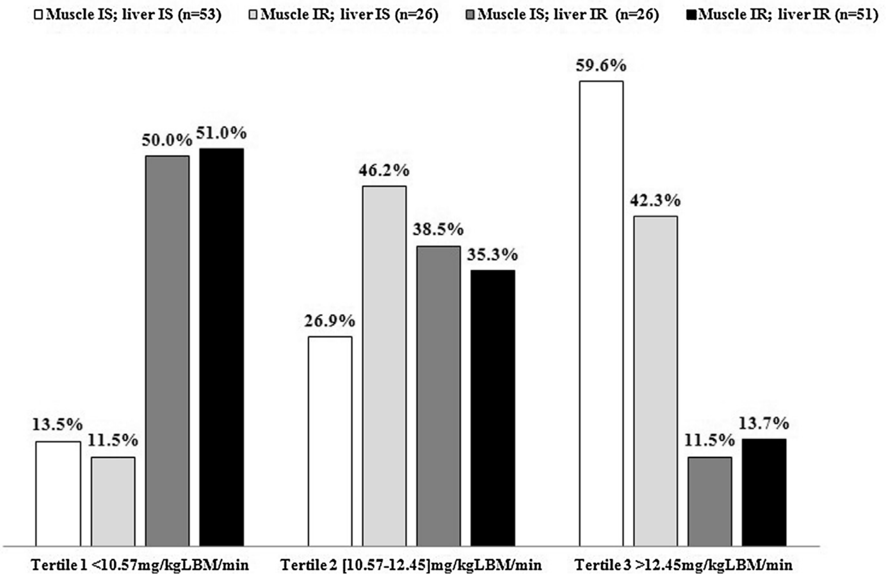

Fig. 4. Classification of postmenopausal women ($N = 156$) according to tertiles of glucose disposal rates (clamp) and type of insulin sensitivity and insulin resistance; $P < 0.001$. IS: insulin sensitive, IR: insulin resistant.

high dose of insulin (i.e. 75 mU.m^{-2}.min^{-1}). Thus, our measurement of whole-body insulin probably reflected more skeletal muscle utilization (but not exclusively) than liver's and the discordance between the assessment of liver and muscle IS/IR was expected (Fig. 4). However, 42.3% of the subject of the highest IS tertile as determined with the clamp technique were classified as liver IS and muscle IR. We could speculate that this subgroup of post-menopausal overweight and obese women, even though classified as muscle IR by the Abdul-Ghani muscle IR index, might have greater skeletal muscle ability for glucose uptake. Therefore, the remained muscle IS is efficient enough to help display high whole-body IS in presence of liver IS.

Previous studies using animals models with isolate muscle IR or liver IR had suggested difference in muscle vs. liver IR for dysglycemia and diabetes development [23,24]. Indeed, the tissue-specific muscle insulin receptor knockout (MIRKO) mouse does not develop hyperinsulinemia or diabetes despite muscle IR [23] while the Liver-specific insulin receptor knockout (LIRKO) mouse displays dysglycemia and progressive liver function impairment [24]. The MIRKO mouse demonstrated a development of adaptive mechanisms in white adipose tissue to compensate for muscle IR to maintain glucose homeostasis while LIRKO mouse was unable to respond to hyperinsulinemia. Even though our findings seem to be in line with the results reported on these investigations with MIRKO and LIRKO

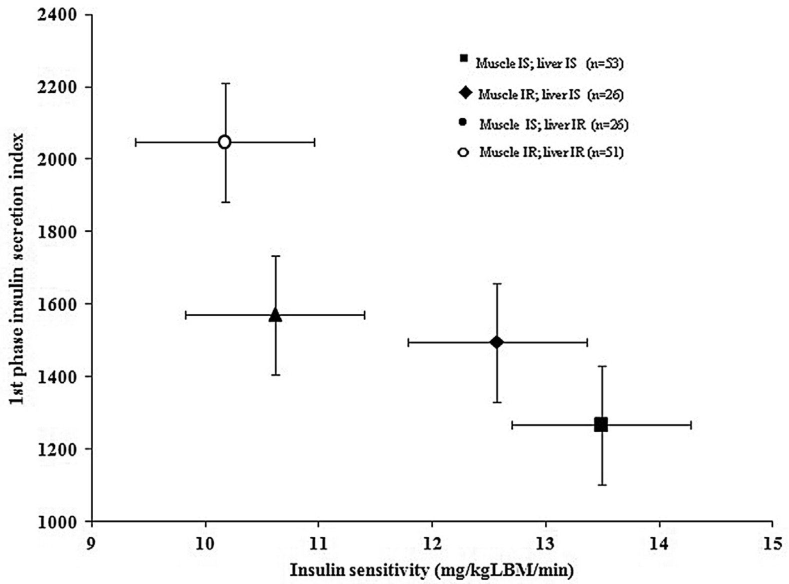

Fig. 5. Disposition index in postmenopausal women ($N = 156$) according to type of insulin sensitivity and insulin resistance ($N = 156$). IS: insulin sensitive, IR: insulin resistant.

mouse, it should be noted that we did not have direct measurement of muscle and hepatic IR. Moreover, adipose tissue function has not been investigated. However, we used validated surrogate indices.

4.2. Insulin resistance and body composition

We determined the relationship between liver vs. muscle IR and body composition. For similar total FM and BMI, liver IR subjects had more VAT than muscle IR subjects. Accumulation of VAT often indicated fat accumulation in other ectopic sites such as liver and muscle. Accordingly, the FLI, a liver fat accumulation index, was higher in liver IR than muscle IR. Increased ectopic fat, which is considered as a consequence of adipose tissue dysfunction, has been associated with IR independently of overall obesity [25]. More specifically, evidences suggest an association between liver lipid synthesis alteration, insulin signalling and liver IR [26]. Thus in the present study participants with high VAT probably had liver fat infiltration and related liver IR. It should be noted that fat infiltration in muscle has not been measured in the present investigation, however, Grunnet et al. [27] have reported that muscle TG content is also associated with hepatic but not peripheral IR in elderly twins.

4.3. Insulin resistance and cardiometabolic risk factors

Our results showed that liver IR was more related to cardiometabolic abnormalities such as altered lipid profile and higher inflammation state than muscle IR. Due to the coexistence of hyperinsulinemia with ectopic fat accumulation, it is difficult to isolate the role of liver IR in these metabolic impairments. Another investigation using the LIRKO mouse has shown that liver IR alone is sufficient to produce dyslipidemia and increased risk of atherosclerosis [28]. Nevertheless, in the present study the impaired metabolic state in the participants with liver IR could be a resultant of the combined effect of liver IR and/or related to ectopic fat accumulation.

Our data did not allow explaining why some individuals would have muscle IR rather than liver IR or both IR. More studies are needed to better understand those observations. It is also important to determine what kind of lifestyle intervention is more appropriate to improve IS in each phenotype. Even though pancreas β-cell mass and function is important in the development of dysglycemia and type 2 diabetes [29], clinical studies have demonstrated the significant effect of lifestyle intervention in IS improvement and the risk to develop type 2 diabetes [30].

Therefore screening for the presence of IR and specifically liver IR should remain a key tool in the prevention of type 2 diabetes as well as associated cardiovascular events among high risk non-diabetics individuals such as those with obesity.

Our study results are supported by the use of gold standard methods to evaluate whole-body IR, glucose tolerance and visceral fat. However, we did not measure direct hepatic glucose production as well as IR and fat infiltration in the skeletal muscle has not been measured.

In conclusion, we demonstrated among a sample of non-diabetic postmenopausal overweight and obese women that liver IR was related to higher prevalence of dysglycemia than muscle IR. Moreover, liver IR was also associated with ectopic fat accumulation, lipid profile alteration and sub-chronic inflammation state.

Disclosure of interest

The authors declare that they have no competing interest.

Acknowledgements

Funding was obtained from Canadian Institutes of Health Research (CIHR) (MONET project) & Genome Canada (CAO project) operating grants as well from the J-A DeSève research chair awarded to Rémi Rabasa-Lhoret. Belinda Elisha & Rémi Rabasa-Lhoret are supported by a Vanier and Fonds de Recherche en Santé du Québec (FRQ-S) scholarships respectively. Katherine Chabot holds a Canadian Institutes of Health Research (CIHR) scholarship. We are grateful to participants that were involved in these two projects.

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Annales d'Endocrinologie
Annals of Endocrinology

Annales d'Endocrinologie 78 (2017) 9–13

Original article

Stroke disclosing primary aldosteronism: Report on three cases and review of the literature

Accident vasculaire cérébral révélant un hyperaldostéronisme primaire : à propos de trois cas et revue de la littérature

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Abstract

Objectives. – There is a growing evidence of increased risk of cerebrovascular events in primary aldosteronism (PA). Nevertheless, acute neurologic ailment as presenting feature of PA is uncommon. Our aim is to highlight the diagnosis challenges in stroke unmasking PA and to discuss the underlying physiopathology and management dilemmas. *Materials and methods.* – We hereby describe three consecutive rare cases of stroke revealing PA. All patients had brain imaging and thorough biological and morphological assessment to rule out other etiologies of stroke. The diagnosis of primary aldosteronism was established according to the Endocrine Society Clinical Practice Guideline, with a review of the literature on the spectrum of neurologic manifestations in PA. *Results.* – We report on three cases, two women and a man, presenting with ischemic or hemorrhagic stroke, of early onset in two of them. All of the reported patients had hypertension and hypokaliemia. This association prompted the assessment of renin angiotensin aldosterone system (RAAS) disclosing PA, which was due to bilateral adenomas in the first one or bilateral adrenal hyperplasia in the two others. All patients refused the surgical option and received spironolactone with recurrence of stroke in one of them due to treatment incompliance. *Conclusion.* – Although cerebrovascular events are quite common in PA, their occurrence as initial feature can be misleading. The association of hypokaliemia and refractory hypertension in ischemic or hemorrhagic strokes should prompt an assessment of the RAAS to rule out PA and initiate adequate management as soon as possible in order to avoid further complications.
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Keywords: Aldosteronism; Stroke; Ischemic; Hemorrhage

Résumé

But/objectif. – Le risque accru d'évènements cérébro-vasculaires est de plus en plus reconnu dans l'hyperaldostéronisme primaire (HAP). Cependant, la survenue inaugurale de manifestations neurologiques aiguës demeure inhabituelle dans l'HAP. Notre objectif était de mettre en évidence les difficultés diagnostiques des accidents vasculaires cérébraux (AVC) révélant un HAP et d'en discuter les mécanismes physiopathologiques et la prise en charge. *Matériels et méthodes.* – Nous décrivons trois cas d'AVC révélant un HAP. Tous les patients avaient eu une imagerie cérébrale et un bilan biologique et morphologique exhaustif afin d'éliminer toute autre cause d'AVC. Le diagnostic d'HAP a été établi selon les recommandations de l'Endocrine Society Clinical Practice Guideline, avec revue de la littérature du spectre de troubles neurologiques dans l'HAP. *Résultats.* – Nous rapportons trois cas, deux femmes et un homme, se présentant avec un tableau d'AVC ischémique ou hémorragique inaugural, à début précoce chez deux d'entre eux. Tous avaient une hypertension artérielle (HTA) et une hypokaliémie. Devant cette association, l'étude du système rénine-angiotensine-aldostérone (SRAA) avait révélé un HAP, dû à des adénomes surrénaliens bilatéraux dans le premier cas ou à une

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http://dx.doi.org/10.1016/j.ando.2016.07.993
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hyperplasie surrénalienne bilatérale chez les deux autres. Tous les patients ont refusé la chirurgie et ont donc reçu la spironolactone avec une récidive hémorragique chez l'un d'entre eux due à une mauvaise observance du traitement antihypertenseur. *Conclusion.* – Malgré la fréquence des évènements cérébro-vasculaires dans l'HAP, leur survenue comme manifestation inaugurale peut être déroutante. L'association d'une hypokaliémie et d'une HTA réfractaire dans les AVC ischémiques et hémorragiques doit faire pratiquer une étude du SRAA à la recherche d'un HAP et initier la prise en charge adéquate afin d'éliminer d'autres complications.

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Mots clés : Hyperaldostéronisme ; Accident vasculaire cérébral ; Ischémie ; Hémorragie

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1. Introduction

Primary aldosteronism (PA), first described by Conn in 1955 [1], is defined as autonomous overproduction of the mineralocorticoid hormone aldosterone, leading to resistant hypertension with or without hypokalemia [2,3]. PA can be due to aldosterone-producing adenomas, bilateral adrenal hyperplasia [3], or more rarely, to adrenocortical carcinoma. While the majority of cases of PA are sporadic, forms of familial hyperaldosteronism have been also described [4]. Currently, there is a growing evidence of increased risk of cardiovascular and cerebrovascular events in PA [5,6].

2. Methods

We hereby describe three consecutive rare cases of stroke revealing PA and discuss their underlying physiopathology, diagnosis challenges and management dilemmas with a review of the literature.

3. Results

3.1. Case 1

A 58-year-old man, with no peculiar family or personal history, presented with sudden onset weakness of the right limbs and slurred speech. On examination, he had drowsiness, Broca's aphasia and right hemiparesis with persisting high blood pressure. Brain CT scan showed left capsulolenticular hematoma (Fig. 1A). The transthoracic echocardiography (TTE), holter monitor (HM), carotid and vertebral Doppler ultrasound (CVDU) were all normal. Laboratory investigations revealed hypokalemia at 2.1 mmol/l (Normal: 3,5 to 5 mmol/l). In search of the cause of hypokalemia, we performed a simultaneous measurement of plasma aldosterone concentration (PAC) and direct renin (DR), in the morning, more than 2 hours after awakening, after 5 to 15 min of seated posture, and discontinuation of interfering medication. We found an increased PAC at 758 pmol/l (Normal: 8–172 pmol/l) with a low DR at 1.5 mIU/l (Normal: 2.8–39,9 mIU/l) and an elevated aldosterone-renin ratio (ARR) at 152 (Normal < 64). These findings were confirmed by a second assessment. An associated corticism was ruled out with normal 24 hour urine free cortisol level and midnight serum cortisol level. An abdominal CT-scan with CT angiography of the renal arteries showed no renal artery stenosis, but disclosed bilateral benign adenomas (Fig. 1B). The diagnosis of hemorrhagic stroke due to hypertension revealing primary aldosteronism, probably due to benign adrenal adenomas was established according to the Endocrine Society Clinical Practice Guideline (Funder et al., 2016). The patient first received intravenous nicardipine with electronic syringe driver then an association of oral spironolactone (200 mg/day) and nicardipine (150 mg/day). On follow-up, he had a normalization of his blood pressure and an improvement of his hemiparesis.

3.2. Case 2

A 47 year-old woman had family history of stroke and personal history of diabetes. At the age of 39, she had acute onset right hemiparesis and dysarthria. Brain CT showed ischemic stroke of the left posterior limb of the internal capsule. In addition, she had persistent severe high blood pressure. On the preliminary laboratory tests, she had hypokaliemia at 2 mmol/l. The HM, CVDU and TTE showed no abnormalities except for left ventricular hypertrophy in the latter. Immunologic and thrombophilia testing were normal. PAC was increased at 740 pmol/l with low DR at 0.17 mIU/l and increased ARR at 340 (Normal < 64). An abdominal CT-scan with CT angiography of the renal arteries showed bilateral adrenal hyperplasia without renal artery stenosis (Fig. 1D). She received spironolactone (200 mg/day), moxonidine (0.4 mg/day) and aspirin (250 mg/day) with an improvement of her motor deficit and her blood pressure. Seven years later, she had a second episode of left hemiparesis. The anamnesis disclosed incompliance to antihypertensive drugs. Brain CT-scan showed a right capsulolenticular hematoma (Fig. 1C). Antiplatelets were ceased and antihypertensive therapy reintroduced with normalization of her blood pressure.

3.3. Case 3

A 42 year-old woman had personal history of resistant non-explored hypertension since the age of 29. She was admitted for sudden onset left hemiparesis. Her brain CT scan and brain MRI showed ischemic stroke of the posterior limb of the right internal capsule and extensive leukoaraiosis (Fig. 1E and G). Brain magnetic resonance angiography (MRA) showed three intracranial aneurysms (Fig. 1H). The HM, CVDU and TTE showed no abnormalities except for left ventricular hypertrophy in the latter. Laboratory findings revealed hypokalemia (1.9 mmol/l).

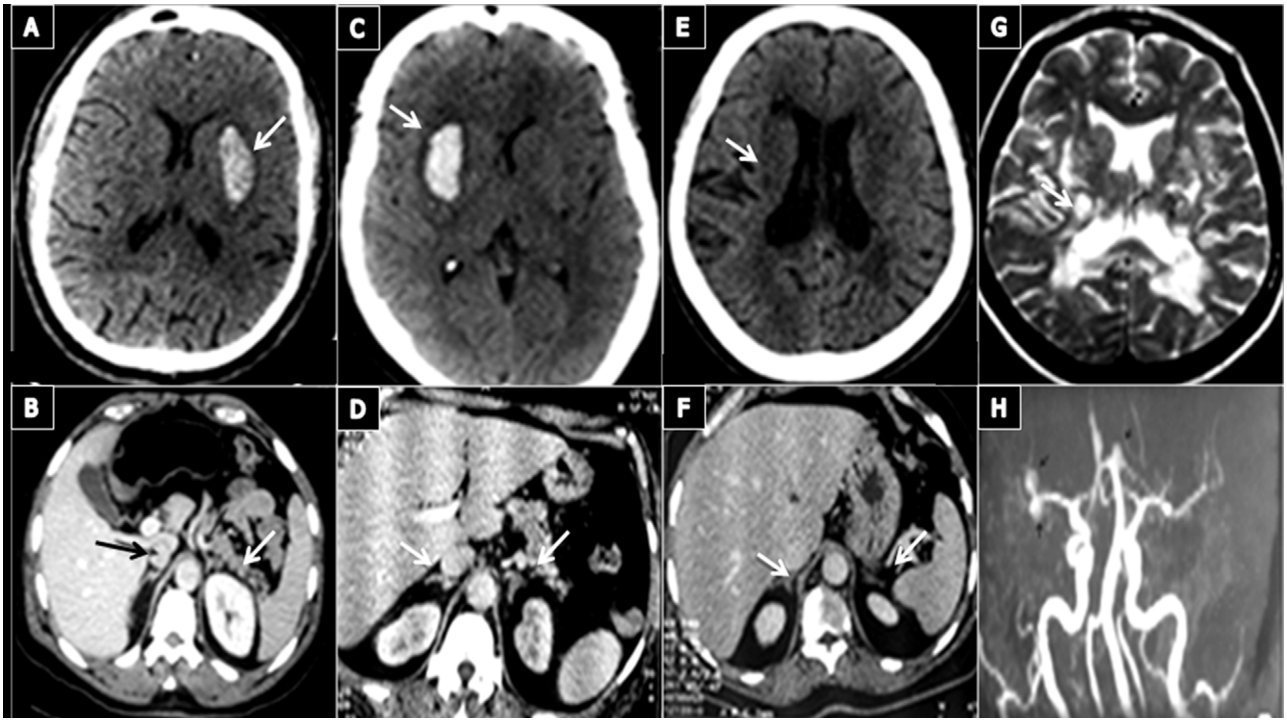

Fig. 1. Imaging of patients with stroke and primary aldosteronism. A, C, E, G and H: brain imaging including CT-scan showing left (case 1) (A) and right (case 2) (C) capsulolenticular hematoma and right capsular ischemic stroke (case 3) (E), also visualized on T2 axial brain MRI associated to periventricular leukopathy (G) and multiple aneurysms of the middle cerebral artery and the basilar trunk on magnetic resonance angiography (H). B, D and F: abdominal CT-scan showing bilateral benign adenomas (B) and adrenal hyperplasia (D and F).

PAC was increased at 806 pmol/l with a low DR at 2.2 mIU/l and an increased ARR at 366 (Normal < 64). An abdominal CT-scan with CT angiography of the renal arteries showed bilateral adrenal hyperplasia without renal artery stenosis (Fig. 1F). She received captopril (150 mg/day), spironolactone (150 mg/day) and nicardipine (150 mg/day) with improvement of her blood pressure levels. She also had an interventional radiological treatment for her unruptured intracranial aneurysms.

4. Discussion

We report on three cases of stroke of early onset in the second and the third patients unmasking primary aldosteronism [2,7] due to bilateral adenomas in the first one or bilateral adrenal hyperplasia in the two others. There is a broad range of neurologic manifestations associated to PA (Table 1) [5,6,8–27]. Nevertheless, acute neurological ailment as presenting feature of PA is extremely rare [28]. All of the reported three patients had hypertension and hypokaliemia. This association prompted the assessment of renin angiotensin aldosterone system in our patients disclosing PA. In fact, PA is the most common secondary cause of hypertension, affecting at least 8–10% of all hypertensive patients and 20% of resistant hypertension [6]. Hypokalemia, influencing the clinical presentation of PA, is found in 50–74% of patients with aldosterone-producing adenoma, and only in 5–17% of patients with idiopathic bilateral hyperplasia [6]. Many recent series revealed an increased rate of cerebrovascular events comprising ischemic and hemorrhagic strokes, both found in our patients, in large populations of PA patients compared with matched essential hypertensive patients (12.9% versus 3.4%) [9,10]. The prevalence of cerebrovascular events in PA patients was approximately 10%–20% and the incidence rate of stroke was 35 cases per 1000 person–years. Currently, several studies shed lights on the pathogenic mechanisms involved and the detrimental role of aldosterone in the cardiovascular and cerebrovascular systems. These studies have shown that aldosterone per se has a pernicious impact on cerebrovascular comorbidity increasing vascular damage independently from its effects on blood pressure levels [9,10]. It is reasonable to conclude that there are three main physiopathological mechanisms underlying the occurrence of stroke in PA. The first is high blood pressure. In fact, during hypertension stimulation, the inward remodelling in the cerebral vasculature may lead to increased arterial stiffness and reduced lumen diameter, consequently impairing the ability of the cerebral vessel to dilate in response to ischemia causing stroke [10]. The second mechanism is the specific effect of aldosterone [9,10]. In fact, it can have a direct effect vasculotoxic in the kidneys and brain, inducing fibrosis by a local effect on both in myocardial and vascular level, with increased intima-media thickness of the vessels, a decrease in endothelial function and microangiopathy [9,10,29,30]. Furthermore, this fibrosis predisposes to formation of microaneurysms, as in our third patient, with an increased risk of hemorrhagic stroke when ruptured [21]. Finally, the third mechanism of stroke occurrence in PA consists of cardiovascular complications. In fact, aldosterone leads to an increase of the thickness of the left ventricle and myocardial fibrosis with possible cardiac arrhythmia [6,10,31]. Chronically elevated

Table 1
Neurological manifestations of primary aldosteronism: review of the literature [5,6,8–27].

Neurological manifestations of primary aldosteronism	
Central	Peripheral
Ischemic stroke (stroke; prolonged reversible ischemic neurological deficit; transient ischemic attacks); cerebral small vessel disease (lacunar infarction, intracerebral hematoma); acute cerebral hemorrhage; cerebrovascular stenosis [5,6,8–10]	Hypokaliemic myopathy [22]; necrotizing myopathy with quadriplegia [23]
Intracranial aneurysm [11]	Periodic paralysis, muscle weakness, paraparesis, quadriparesis [22], focal weakness (one leg, one hand) [24]
Dementia, consciousness disturbance [5], coma [12]	Myalgia, aching pain of the lower limbs, cramps, tetany [25]
Hemiparesis; dysarthria [5]	Rhabdomyolysis (with concurrent sporadic inclusion body myositis)[*] [26]
Epilepsy/seizures (generalized and partial)[*] (primary aldosteronism, seizures and neurological abnormalities [PASNA]) [13,14]	Myasthenia gravis[*] [27]
Cerebral palsy[*] (PASNA) [14]	
Cortical blindness[*] (PASNA) [14]	
Athetosis[*] [14]	
Headache [15]	
Idiopathic intracranial hypertension [16]	
Psychiatric disorders (depression, generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, demoralization, persistent somatization, irritable mood, stress, lower physical well-being, episodic rage attacks) [17–19]	
Sleep disorders (obstructive sleep apnea, excessive daytime sleepiness, poor sleep quality) [20]	
Anterior ischemic optic neuropathy [21]	

[*] Probable fortuitous association.

blood pressure plays a role in the pathogenesis of left ventricular hypertrophy [10]. A retrospective case-control study of Kao et al. showed that PA patients with proteinuria, a history of coronary artery disease or left ventricular hypertrophy as found in two of our patients, and spironolactone in use at diagnosis are associated with an increased risk of de novo ischemic stroke [10]. Appropriate correction of aldosterone and normalization of blood pressure can reverse left ventricular hypertrophy and possible other end organ damage at long-term. More intensive blood pressure strategy might be advocated to avoid the target organ damage [10]. Treatment of PA is focused at prevention of morbidity following long duration of hypertension and aldosterone induced organ damage. Spironolactone is aimed at antagonizing mineralocorticoid and helps improve hypokalemia in half PA patients, used in all three cases of our report [10]. In the second line, amiloride can be suggested, as are other conventional antihypertensive drugs if blood pressure levels remain uncontrolled. In case of bilateral adrenal hyperplasia or adenomas as in our three patients, surgery aims to control the consequences of hypersecretion, rather than the oncologic aim in adrenocortical carcinoma. Young patients, as our second and third patients, have long-life expectancy and low anesthesia-related risk, and are thus ideal candidates for surgery. It is important to distinguish PA with lateralized and non-lateralized secretion. In the latter, management is only medical. Hence, etiological exploration distinguishes candidates for adrenalectomy in case of lateralized PA and those (non-lateralized) in which it would serve no purpose. Prior to adrenal vein sampling (AVS), treatment decision should be discussed. AVS is pointless in patients unwilling to undergo surgery, as our patients who refused the surgical option [4].

5. Conclusion

Our study highlights the diagnosis challenges in atypical presenting forms of PA. Although cerebrovascular events are quite common in PA, their occurrence as initial feature can be misleading. The association of hypokaliemia and refractory hypertension in ischemic or hemorrhagic strokes should prompt an assessment of the renin angiotensin aldosterone system to rule out PA and initiate adequate management as soon as possible in order to avoid further complications.

Disclosure of interest

The authors declare that they have no competing interest.

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Annales d'Endocrinologie
Annals of Endocrinology

Annales d'Endocrinologie 78 (2017) 14–19

Original article

Usefulness of a systematic screening of carotid atherosclerosis in asymptomatic people with type 2 diabetes for cardiovascular risk reclassification

Utilité du dépistage systématique de l'athérosclérose carotidienne chez les sujets diabétiques de type 2 asymptomatiques pour le reclassement du risque cardiovasculaire

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Abstract

Aims. – Routine screening of carotid atherosclerosis lesions is frequently suggested for people with type 2 diabetes, the presence of a carotid lesion being associated with a significant increase risk for vascular events. However, the impact of this strategy on medical management is not validated. We herein question the usefulness of such screening. *Methods.* – We assessed the prevalence and severity of carotid lesions in 337 consecutive people with type 2 diabetes without known cardiovascular disease who underwent a systematic carotid duplex ultrasonography. We analyzed whether the results of duplex ultrasonography allowed reclassification of cardiovascular risk level relative to the most recent international recommendations on diabetes and modified therapy. *Results.* – We found that 35.9% of people had no atherosclerotic lesion. Prevalence of carotid stenosis $< 20\%$, between 20 and 50% and $\geq 50\%$ were 32.9%, 28.4% and 2.7% respectively. Regarding the use of statins and LDL-C target, the result of carotid duplex ultrasonography allowed to reclassify respectively 11.8% to 55.2% of the cohort in a higher cardiovascular risk level. For the indication of antiplatelet agent, reclassification in a higher risk level concerned 6.8% of the patients. No subject had an indication of carotid revascularization. *Conclusions.* – Carotid atherosclerosis is frequent in asymptomatic people with type 2 diabetes in primary cardiovascular prevention. Screening for carotid atherosclerosis by duplex ultrasonography seems useful to redefine the level of cardiovascular risk.
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Keywords: Cardiovascular prevention; Carotid atherosclerosis; Carotid duplex ultrasonography; Type 2 diabetes

Résumé

Objectifs. – Le dépistage systématique des lésions athéromateuses carotidiennes est souvent réalisé en routine chez les sujets diabétiques de type 2 asymptomatiques, la présence d'un athérome carotidien étant associé à un surrisque important d'événements vasculaires. Cependant, l'impact de cette stratégie dans l'optimisation de la prise en charge des patients n'est pas validé. L'objectif de cette étude est de s'interroger sur l'utilité d'un tel dépistage. *Méthodes.* – Nous avons évalué la prévalence et la gravité des lésions carotidiennes par écho-doppler chez 337 patients diabétiques de type 2 consécutifs en prévention cardiovasculaire primaire. Nous avons regardé si les données du doppler artériel permettaient

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Abbreviations: CCA, Common carotid artery; CVD, Cardiovascular disease; DUS, Duplex ultrasonography; ICA, Internal carotid artery.

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http://dx.doi.org/10.1016/j.ando.2016.12.001
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une reclassification du niveau de risque cardiovasculaire par rapport aux recommandations internationales de 2016 et modifiaient la prise en charge thérapeutique. *Résultats.* – Nous avons constaté que 35,9 % des personnes n'avaient aucune lésion athéromateuse. La prévalence des lésions carotidiennes < 20 %, entre 20 et 50 % et ≥ 50 % étaient respectivement de 32,9 %, 28,4 % et 2,7 %. Concernant l'utilisation des statines et la cible de LDL-C, le résultat du doppler carotidien a permis de reclasser respectivement 11,8 % à 55,2 % de la cohorte à un niveau de risque cardiovasculaire plus élevé. Pour l'indication d'un antiagrégant plaquettaire, un reclassement à un niveau de risque supérieur a concerné 6,8 % des patients. Aucun sujet n'avait d'indication de revascularisation carotidienne. *Conclusions.* – L'athérome carotidien est fréquent chez les sujets diabétiques de type 2 asymptomatiques en prévention cardiovasculaire primaire. Le dépistage systématique de l'athérome carotidien par écho-doppler semble utile pour redéfinir le niveau de risque cardiovasculaire.

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Mots clés : Prévention cardiovasculaire ; Athérome carotidien ; Écho-doppler ; Diabète de type 2

1. Introduction

Atherosclerosis complications are the main leading cause of mortality and disabling in people with diabetes. Despite a reduction in the rate of cardiovascular disease (CVD) in recent years, the risk of events in people with diabetes is still two times that in individuals without diabetes [1].

Different methods have been used to better predict the risk of vascular events, such as the UKPDS risk score [2]. However, the validity of these scores depends on the population studied, and their utility as a way of improving the effectiveness of primary vascular prevention interventions is not well studied [2]. Besides these risk scores, the presence of an existing carotid atherosclerosis is associated with the risk of stroke in the general population and in people with diabetes, as well as with the risk of cardiovascular events [3–6]. Several studies have showed that the use of carotid duplex ultrasonography (DUS) to detect subclinical atherosclerosis allowed a much more accurate identification of high-risk individuals than CVD risk score [7–9]. In that way, the last European guidelines on cardiovascular prevention note that carotid artery plaque assessment using DUS may be considered to be a risk modifier in CV risk prediction in some cases [2]. Even if diabetes is an independent risk factor of carotid atherosclerosis, and in particular for advanced stenosis [10,11], only a few studies are available concerning the prevalence of carotid atherosclerosis in asymptomatic patients in primary cardiovascular prevention [12,13] and there is no specific data available concerning the impact of carotid DUS to reclassify the CVD risk in this population.

However, there is no consensus to recommend a systematic screening of carotid arteries in asymptomatic people with diabetes [2,14,15]. In contrast, this screening is actively carried out in clinical practice on the free appreciation of medical doctors that it may be useful. There are, at the time, no validated tools to determine who is at increased risk of carotid atherosclerosis stenosis and, when atherosclerosis is present, who is at increased risk for stroke [15]. The main goals of this screening are, firstly, to evaluate the prevalence of surgical stenosis; secondly, to better assess the cardiovascular risk profile in people with diabetes and, lastly, to improve the prevention therapy. A medical therapy including a lipid lowering therapy, antiplatelet treatment and an optimal blood pressure are recommended in cases of carotid atherosclerosis, whatever the degree of stenosis or the symptomatic character of the lesion [16].

Therefore, the aim of the study was to assess the additional value of the screening of carotid atherosclerosis by DUS on CVD risk classification and the impact on medical strategy in a cohort of patients with type 2 diabetes without known cardiovascular disease.

2. Methods

2.1. Patients

The study involved 337 people with type 2 diabetes in primary cardiovascular prevention who had a routine screening by carotid artery DUS between January 2012 and December 2012, in a single vascular medicine department. All people had had a recent evaluation of diabetes complications. Patients with a history of coronary vascular disease or cerebral infarction were excluded, as were people with a known peripheral artery disease. Current smoker was defined as active smoking during the past 3 years. High blood pressure was defined as ≥ 140/85 mmHg [2]. The study was approved by the local institutional committee of Hospices Civils de Lyon (no. 15-021).

2.2. Carotid duplex ultrasonography

Both carotid arteries were examined using a B-mode ultrasound Antares (Siemens) equipped with a 7–10 MHz high-resolution probe, and operated by a trained technician. Peak systolic velocities were measured in the common carotid artery (CCA), bulb and internal carotid artery (ICA). A diagnosis of stenosis was rendered when velocity criteria consistent with the existence of plaques and the narrowing of the lumen were observed. The velocities cut off described above permit to estimate the degree of stenosis with a good correlation to NASCET criteria [17].

The most severe lesion for each people was selected. Subjects were classified as normal (no atherosclerotic lesions), stenosis < 20% or < 2 mm of plaques thickness, stenosis > 20% and < 50% (ICA/CCA systolic ratio ≤ 2) and stenosis ≥ 50% (ICA/CCA systolic ratio > 2). A stenosis ≥ 70% was defined by ICA/CCA systolic ratio > 4 [17].

2.3. Cardiovascular risk classification, indications of statin, antiplatelet agent and LDL-C goal according to guidelines [2,14]

ADA guidelines 2016 recommend when to initiate and intensify statin therapy (high vs. moderate intensity) based on cardiovascular risk profile. Patients were stratified into the following age-groups: < 40, 40–75 and > 75 years old. Additionally, individuals were stratified into high-, intermediate-, and low-risk subgroups (based on age and presence of additional CVD risk factors including LDL-C ≥ 100 mg/dL (2.6 mmol/L), high blood pressure, smoking, overweight and obesity and family history of premature atherosclerotic cardiovascular disease) [14]. These guidelines recommend that aspirin therapy (75–162 mg/day) should be added for people with diabetes as a primary prevention strategy for those at increased cardiovascular risk (10-year risk ≥ 10%: men or women ≥ 50 with one or more CVD risk factors including family history of premature atherosclerotic cardiovascular disease, hypertension, smoking, dyslipidemia, or albuminuria). Clinical judgment should be used for those at a lower CVD risk (10-year risk between 5 to 10%: men or women ≥ 50 without CVD risk factor and men or women < 50 with CVD risk factors) and there is no indication for people with a CVD risk < 5% (men or women < 50 without CVD risk factor). Authors admit the poor level of evidence for this recommendation.

For European guidelines on cardiovascular disease prevention in 2016, people with diabetes and major CVD risk factors (including smoking, marked hypercholesterolemia (≥ 310 mg/dL or 8 mmol/L), marked high blood pressure (≥ 180/110) and/or target organ damage (including clearance < 30 mL/min, proteinuria) were classified in very high-risk group (estimated 10-year risk of a first fatal atherosclerotic event ≥ 10%) and in high-risk group for others patients with type 2 diabetes (estimated risk between 5 to 10%) [2]. A statin should be considered for every people with diabetes above 40 years old whatever the baseline LDL-C level. LDL-C target of < 70 mg/dL (1.8 mmol/L) or at least a ≥ 50% LDL-C reduction if this target goal cannot be reached is recommended in patient with very high-risk and < 100 mg/dL (2.6 mmol/L) for the others. For people < 40 years of age with evidence of end-organ damage or significant risk factors a statin may be indicated but additional guidance on care is needed to confirm that recommendation and to define LDL target. These guidelines did not recommend antiplatelet therapy (aspirin or clopidogrel) for adults with type 2 diabetes without CVD.

2.4. Statistical analysis

Variables were described with mean, standard deviation for continuous variables; counts and percentages for categorical ones. Binary logistic regressions were fitted to study risk factors for presence of carotid atherosclerosis. Pre-specified candidate risk factors were sex, age, duration of diabetes, current smoker, HbA1c, LDL-C, HDL-C, High blood pressure, nephropathy. Tests were considered significant for *P*-values less than 5%. Analyses were performed in SAS 9.3 (SAS Institute, Cary NC).

3. Results

3.1. Characteristics of the population

Main characteristics of the population are described in Table 1. There was a high prevalence of complications, with 56.1% of people with at least one location of microangiopathy. For people with lipid lowering therapy 89.7% were under statins, 10.3% under ezetimibe and 7.5% under fibrates. On the 232 people with blood pressure lowering treatment, 85% were under angiotensin converting enzyme inhibitor or angiotensin II receptor blockers. Three or more blood pressure lowering drugs were used in 29.3% of cases.

3.2. Prevalence of carotid atherosclerosis

The prevalence of carotid atherosclerosis was 64.1%, including 32.9% ($n = 111$) with stenosis < 20%, 28.4% ($n = 96$) with 20–49% stenosis and 2.7% ($n = 9$) with ≥ 50% stenosis. None of them presented a stenosis ≥ 70%.

In multivariate analysis, only age, and HDL-C were significantly associated with the risk of carotid atherosclerosis. At any given age, each additional decade unit of HDL-C decreases the risk of carotid atherosclerosis by 26% (OR = 0.74 [0.60–0.90], $P = 0.003$), while at any given HDL-C level, each additional decade of age multiplies the risk of carotid atherosclerosis by 2.61 ([2.00–3.40], $P < 0.001$).

3.3. Cardiovascular risk classification and therapeutic recommendations

3.3.1. Statin therapy and LDL-C target

According to European guidelines on cardiovascular disease prevention 2016 and ADA guidelines 2016 respectively 96% and 100% of our cohort were indicated statin (Tables 2 and 3).

According to ADA, most of the patients (80.7%) were classified in high-risk patients with an indication of high-intensity statin therapy while 11.6% were classified moderate to high and 7.7% moderate. In patients with moderate and moderate to high-risk, 61.5% (11.8% of the entire cohort) had a carotid lesion and should be reclassified in high-risk patients (Table 2).

For European guidelines on cardiovascular disease prevention a LDL-C target < 70 mg/dL was recommended in 11.6% of patients with very high CVD risk. Among the 83.7% patients with a high CVD risk and a LDL-C target < 100 mg/dL, 65.9% had carotid lesion (including 2.7% with stenosis ≥ 50%) and should be reclassified in very high-risk patients (55.2% of the entire cohort) (Table 3).

3.3.2. Antiplatelet therapy

According to ADA, 80% of patients had an estimated 10-year CVD risk ≥ 10% and an indication to introduce an antiplatelet agent (Table 4). Concerning patients with an intermediate 10-year CVD risk of 5 to 10%, 38.4% had carotid atherosclerosis

Table 1
Demographic characteristics of the population.

Demographic factors	General population $n = 337$	Lesion $n = 216$ (64.1%)	No lesion $n = 121$ (35.9%)
Age (years)	61.1 ± 12.0	66.1 ± 10.8	55.8 ± 12.2
Male sex (%)	55.1	57.9	49.6
Diabetes duration (years)	10.9 ± 9.1	12.1 ± 9.4	8.7 ± 8.4
BMI (kg/m^2)	31.9 ± 7.1	31.5 ± 7.0	32.7 ± 7.2
Current smokers (%)	24.4	23.6	25.6
HbA1c (%)	8.6 ± 2.2	8.7 ± 2.2	8.4 ± 2.2
HbA1c (mmol/mol)	70	73	68
HDL-C (mg/dL)	43.7 ± 12.4	42.8 ± 12.6	45.4 ± 11.7
LDL-C (mg/dL)	109.4 ± 36.5	108.0 ± 37.6	110.0 ± 34.6
High blood pressure (%)	27.3	30.1	22.3
Lipid lowering therapy (%)	54.9	58.8	47.9
Blood pressure lowering therapy (%)	68.8	75.0	57.8
Antiplatelet therapy (%)	23.1	30.5	9.9
Retinopathy (%)	20.1	22.7	15.7
Neuropathy (%)	27.9	32.9	19.1
Nephropathy (%)	37.4	41.2	30.6

Table 2
Recommendations for statin in people with diabetes following ADA guidelines 2016 and result of carotid duplex ultrasonography [14].

Age	Risk factors[a]	Statin dose[b]	Number	Lesion		No lesion
				All	Stenosis ≥ 50%	
Age < 40	Without CVD risk factor	None	0	0	0	0
	With CVD risk factor	Moderate	16	1	0	15
Age 40–75	Without CVD risk factor	Moderate	7	3	0	4
	With CVD risk factor	High	272	176	9	96
Age > 75	Without CVD risk factor	Moderate	3	1	0	2
	With CVD risk factor	Moderate or high	39	35	0	4

[a] CVD risk factors include LDL cholesterol ≥ 100 mg/dL (2.6 mmol/L), high blood pressure, smoking, overweight and obesity, and family history of premature atherosclerotic cardiovascular disease.

[b] In addition to lifestyle therapy.

Table 3
Recommendations for statin and LDL-C target in people with diabetes following European guidelines on cardiovascular disease prevention 2016 and result of carotid duplex ultrasonography [2].

Age	Risk factors[a]	Statin	LDL-C target	Number	Lesion		No lesion
					All	Stenosis ≥ 50%	
Age < 40	No	No	ND	13	0	0	13
	Yes	Yes	ND	3	1	0	2
Age ≥ 40	No	Yes	< 100 mg/dL(2.6 mmol/L)	282	186	5	96
	Yes	Yes	< 70 mg/dL (1.8 mmol/L)	39	29	4	10

[a] CVD risk factors include smoking, marked hypercholesterolemia (≥ 310 mg/dL or 8 mmol/L), marked high blood pressure (≥ 180/110) and/or target organ damage include clearance < 30 mL/min, proteinuria.

Table 4
Recommendations for antiplatelet agent in people with diabetes following ADA guidelines 2016 and result of carotid duplex ultrasonography [14].

		Number	Lesion		No lesion
			All	Stenosis ≥ 50%	
Indications for an antiplatelet agent	CVD risk ≥ 10% at 10 years	270	193	9	74
Possible indications for an antiplatelet agent	CVD risk between 5 to 10% at 10 years	66	23	0	38
No indication for an antiplatelet agent	CVD risk < 5% at 10 years	1	0	0	1

CVD: cardiovascular disease.

and should be reclassify in high-risk patients (6.8% of the entire cohort).

4. Discussion

We described the prevalence of carotid atherosclerosis in a cohort of people with type 2 diabetes and analyzed the impact on reclassification for cardiovascular risk, statin and antiplatelet needs, or change in LDL-C target.

The first message of our study is that carotid atherosclerosis is frequent in a recent cohort of asymptomatic people with diabetes, without known cardiovascular disease, despite significant progress in cardiovascular prevention management in recent years. Indeed, the prevalence of carotid atherosclerosis in our study was similar to results observed in older cohorts despite some variations in the diagnostic criteria [12,13].

The second point is that new recommendations on cardiovascular prevention in diabetes recommend prescription of statins in all patients with carotid atherosclerosis. We observed that a systematic screening of carotid atherosclerosis by DUS permit to reclassify the cardiovascular risk of some patients. Some studies showed that the risk of CVD events is twice more important in patients with subclinical carotid atherosclerosis than in patients without lesions [4–6]. In the CAFES-CAVE study, 10,000 patients with low CVD risk were followed during 10 years [3]. If the rate of CVD events at 10 years was as expected low at 0.12% in patients with normal carotid wall, it increased at 8.6% in those with carotid wall thickening, 39.3% in those with non-stenosing plaque and 81% in patients with stenosing plaque. So, patients with subclinical carotid atherosclerosis present a high-risk of CVD events and must probably benefit for an intensive cardioprotective treatment with antiplatelet agent, high intensity statin therapy and low LDL-C target. It can be underline, that there is at that time no data on literature to suggest that patients with a recommended moderate-intensity statin therapy, mainly > 75 years old in our study, could benefit for higher intensity level. In the same way, there is no evidence that these patients should have a LDL-C target < 70 mg/dL and interventional studies are needed to confirm that strategy.

Concerning antiplatelet agent, indication in primary prevention is controversy in guidelines [2,14]. In our study, 19.6% of patients had an intermediate estimated 10-year CVD risk between 5 and 10% and so an indication left to clinical judgment. In those patients, 38.4% (6.8% of the entire cohort) had a carotid atherosclerosis and should be reclassified in high-risk patients with antiplatelet agent indication. To understand discrepancies between guidelines, one can bear in mind that although antiplatelet treatment significantly decreases the risk of vascular events in secondary prevention, the benefit is less clear in primary prevention, with a 12% reduction of the risk of a vascular event, without any effect on stroke and no significant effect on people with diabetes [18]. Moreover, under this treatment, the presence of diabetes was associated with a 50% increased risk of major extracranial bleeds [2]. So, the benefit/risk of antiplatelet therapy suggests caution in people with an intermediate 10 years cardiovascular risk. In that way, contrary to previous guidelines, new European guidelines on cardiovascular disease prevention did not recommend anymore antiplatelet treatment in primary prevention [2]. So, carotid screening by DUS could be a useful tool to better select patients with the higher risk of CVD and guide the prescription of antiplatelet agent.

Regarding surgery, 2.7% of our population had a carotid atherosclerosis stenosis ≥ 50% but none of them had a lesion ≥ 70%. In our cohort, all of them have an indication of an optimal medical therapy including high-intensity statin and antiplatelet agent according to guidelines. Moreover, even for the population with asymptomatic carotid lesion ≥ 70% the 10-year risk of a CVD event has decreased nowadays around 10% under an optimal cardiovascular prevention treatment and revascularization for asymptomatic people is probably no more indicated with contemporary stroke prevention medical therapy [19,20].

Our study has some limitations, including those inherent to a retrospective observational study design. First, the patients with diabetes studied were all referred to a medical department specifically managing these patients, and therefore, the results obtained here cannot be extended to all subjects with diabetes. Secondly, we have not achieved long-term monitoring for the occurrence of cardiovascular or cerebrovascular clinical manifestations to confirm CVD risk classification in our patients. Last, we did not follow the progression of carotid lesion, which is associated in some studies with a higher risk of cerebrovascular events but also of cardiovascular events [21]. However, we did not confirm this association in a retrospective cohort of diabetic patients despite an annualized progression rate of 3.1% [21]. A prospective study is needed to confirm or not that result.

5. Conclusion

In conclusion, systematic screening of carotid atherosclerosis by DUS seems useful to redefine the level of cardiovascular risk in patients with diabetes in primary cardiovascular prevention. It may help to identify individuals who may benefit from more aggressive therapy for primary prevention, such as low-dose aspirin, high intensity statin therapy and low LDL-C target.

Disclosure of interest

The authors declare that they have no competing interest.

Acknowledgements

The authors thank Lucienne Marmasse for English language support.

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Annales d'Endocrinologie
Annals of Endocrinology

Annales d'Endocrinologie 78 (2017) 20–26

Original article

Treatment by rituximab on six Grave's ophthalmopathies resistant to corticosteroids

Traitement par rituximab de six orbitopathies dysthyroïdiennes résistantes aux corticoïdes

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Abstract

Objectives. – Graves' ophthalmopathy occurs in 50% of Graves' disease cases. Treatment is based on smoking cessation, and control of the euthyroidism and ocular repercussions associated with the disease. The active orbital forms are treated with glucocorticoids. Non-validated therapies have also been recently tested. Rituximab has been effectively used several times to treat corticosteroid-resistant Graves' ophthalmopathy associated with an optic neuropathy, but its use could be proposed only in inflammatory ophthalmopathies after failure of the corticosteroids. We present six cases treated since early 2012 at the University Hospital Center of Tours, France. *Methods.* – Six patients were treated at the University Hospital Center of Tours, France, between September 2012 and April 2014. The patients had a Mourits' score greater than three after treatment with corticosteroids and/or a severe NOSPECS score and/or orbital inflammation resistant to maximal treatment with intravenous injections of methylprednisolone and an optic neuropathy. They twice received one gram of rituximab by slow intravenous injection two weeks apart. Efficacy was assessed by a decrease of the orbital inflammatory clinical Mourits' score, and visual acuity and visual field testing. *Results.* – The inflammatory score of patients improved and treatment helped to stop the progression of the sequelae due to neuropathy. The orbital inflammatory clinical score, and the visual acuity and visual field improved but orbital decompression was necessary to complete the treatment. *Conclusion.* – Rituximab has been used for the treatment of active corticosteroid-resistant Graves' ophthalmopathies. We also had positive results on patients with visual threat and optic neuropathy, when combined with surgical decompression.
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Keywords: Graves ophthalmopathy; Rituximab; Anti-CD20; Optic neuropathy

Résumé

Introduction. – L'orbitopathie basedowienne survient dans 50 % des maladies de Basedow. Son traitement repose sur l'arrêt du tabac, l'euthyroïdie et le traitement du retentissement oculaire (symptômes et séquelles). Le traitement de l'orbitopathie active aiguë repose sur la corticothérapie, cependant plusieurs autres thérapeutiques non validées sont à l'étude. Le rituximab a été utilisé à plusieurs reprises efficacement pour traiter des atteintes orbitaires graves avec atteinte du nerf optique, quand celles-ci étaient résistantes aux corticoïdes, mais son utilisation ne pourrait être proposée que dans l'indication inflammatoire après échec des corticoïdes. Nous présentons ici six cas traités au centre hospitalier universitaire de Tours depuis début 2012. *Matériels et méthodes.* – Six patients ont été traités au centre hospitalier universitaire de Tours entre septembre 2012 et avril 2014, présentant un score de Mourits supérieur à trois, persistant après la corticothérapie, et/ou un score NOSPECS sévère, et/ou avec une inflammation orbitaire résistante à un traitement maximal par bolus de Solumédrol®, et une neuropathie optique. Ils ont reçu un gramme de rituximab en perfusion lente intraveineuse, à deux reprises à deux semaines d'intervalle. L'efficacité a été évaluée sur la diminution du score inflammatoire clinique orbitaire de Mourits, l'acuité visuelle et le champ visuel. *Résultats.* – Les patients traités ont amélioré leur score inflammatoire et le traitement a permis d'éviter l'aggravation des séquelles de la maladie dans les formes avec neuropathie. Le score inflammatoire orbitaire a été amélioré ainsi que l'acuité visuelle et le champ visuel. Un traitement par décompression orbitaire a été nécessaire en complément dans tous les cas.

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http://dx.doi.org/10.1016/j.ando.2016.12.002
0003-4266/© 2016 Published by Elsevier Masson SAS.

Conclusion. – Le rituximab a été utilisé dans les orbitopathies dysthyroïdiennes actives résistantes aux corticoïdes. Nous avons eu également des résultats positifs pour nos patients avec menace visuelle et neuropathie optique résistantes aux corticoïdes, en complément de la décompression chirurgicale.

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Mots clés : Orbitopathie basedowienne ; Rituximab ; Anti-CD20 ; Neuropathie optique

1. Objectives

Graves' ophthalmopathy is a disfiguring and potentially blinding disease, which greatly affects the appearance of patients and their quality of life. It affects the eyelid and the area around the orbit combining proptosis, oculomotor disorders, and eyelid abnormalities. The incidence of Graves' disease is 16 per 100,000 for women and three per 100,000 for men per year [1]. Graves' ophthalmopathy occurs in 50% of these patients and can be severe in 3–5% of cases. The symptoms can range from a sensation of dry eye, photophobia, excessive watering, and binocular diplopia, to damage to the optic nerve resulting in visual loss and/or visual field defects.

Several factors have been found to be associated with the severity of symptoms including being male, thyroid hormonal imbalances [2], and tobacco use, which is the most important modifiable risk factor. Immunosuppressive therapies are also less effective in smokers. The most common clinical manifestations are upper eyelid retraction, edema, erythema of the periorbital tissue and conjunctiva, and proptosis. Symptoms are related to the increase of soft tissue in the orbital cavity associated with mononuclear cell infiltration into the extraocular muscles, lacrimal glands and fat tissue. Disease activity is quantified by the Mourits' clinical inflammatory score [3] amended by the European Study Group on Graves' orbitopathy EUGOGO [4].

The diagnosis of Graves' ophthalmopathy is based on clinical characteristics, but imaging can aide diagnosis; CT evaluates the severity of proptosis, magnetic resonance imaging visualizes the inflamed tissues, and ultrasound quantifies the level of edema and inflammatory cell infiltration.

The infiltrating mononuclear cells are mainly CD4 + T lymphocytes, which are activated by antigen presenting cells such as B cells. These T cells cause a local inflammatory reaction by activating fibroblasts and secreting cytokines such as IL-2, IFN-γ, and TNF. The fibroblasts synthesize hyaluronic acid and some of them differentiate into mature adipocytes. These changes result in a volume increase of muscles and orbital fat. The origin of the orbital location of inflammation is poorly understood; fibroblast proteins acting as autoantigens has been suggested [5].

The standard treatment for Graves' ophthalmopathy is IV glucocorticoid therapy [6]. Rituximab, directed against the CD20+ lymphocyte marker is already used to treat various pathologies, such as non-Hodgkin lymphoma and rheumatoid arthritis. It has been repeatedly used to treat Graves' ophthalmopathies when they were resistant to corticosteroids because of its action against B cells, which strongly contribute to orbital inflammation. It has been effectively used in some cases with optic neuropathy [7–14]. However, its use could be proposed only in inflammatory ophthalmopathies, if corticosteroids have failed, and non-recommended in optic neuropathy according to the last guidelines in 2016 because of the development of optic neuropathy after a rituximab treatment in some cases [6].

We present six cases treated at the University Hospital Center of Tours, France, since early 2012.

2. Methods

Six patients were treated with rituximab between September, 2012 and April, 2014 for Graves' ophthalmopathies at the Tours University Hospital Center, France. They had a Mourits' inflammatory clinical orbital score greater than 3 and were initially treated for inflammatory Graves' ophthalmopathy with glucocorticoid therapy. The protocol consisted of 15 mg/kg intravenous injections (with doses up to 1000 mg) of methylprednisolone every fifteen days for two months and then 7.5 mg/kg every two weeks for two months, with additional treatments if necessary. The cumulative dose did not exceed 8 g due to the risk of liver toxicity, as recommended by the EUGOGO working group [6]. Rituximab treatment was initiated when the patients had a visual threat and an optic neuropathy and were considered to be resistant to glucocorticoids. Indications were a threat to visual function or integrity of the cornea, and neuropathy: decrease of visual acuity, visual field defects, severe corneal damage, uncontrolled inflammation. All patients had a proven or suspected optic neuropathy. Patients received one gram of intravenous rituximab in slow infusion, twice, two weeks apart, in combination with 100 mg of intravenous methylprednisolone, 10 mg of Polaramine®, and 1 g of paracetamol. This protocol has already been reported in the literature [13,14]. Efficacy was evaluated based on the evolution of the Mourits' orbital clinical inflammatory score and on changes of visual acuity or visual field, three to six months after treatment with rituximab. Proptosis and intraocular pressure were also followed. These clinical data were analyzed one month before the patients received rituximab therapy, three to six months after, and at the last follow-up consultation for each patient. The chronology of the treatment protocol for each patient is shown in Fig. 1.

3. Results

The three men and three women of the study all had a thyroidectomy prior to rituximab treatment. One patient did

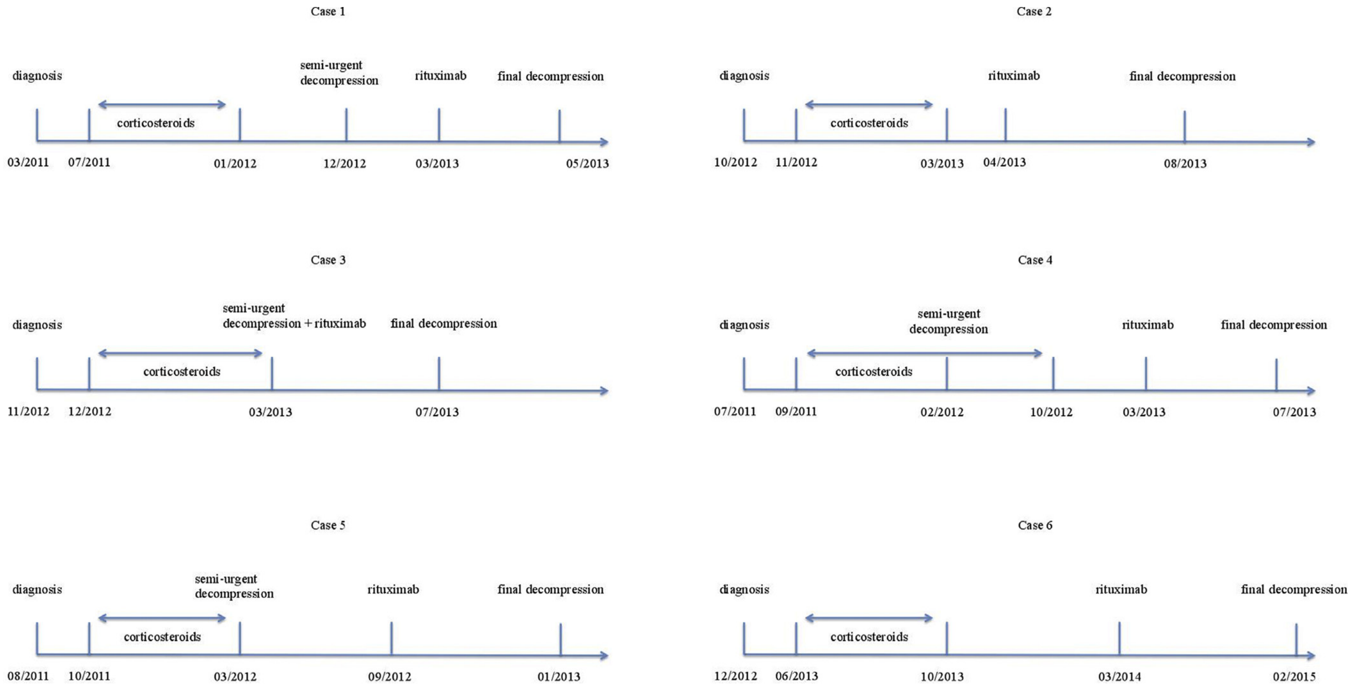

Fig. 1. Chronology of the various treatments: corticosteroids, orbital decompression, rituximab, for case 1 to 6.

not stop smoking prior to treatment. Three patients were non-smokers; the other two were ex-smokers. All patients exhibited oculomotor disorders. Visual acuity was abnormal for four patients. The Mourits' score was greater than or equal to three for five patients. Five patients had proptosis of greater than 18 mm. All six patients had visual field defects. Four patients had emergency decompression surgery (floor and medial wall), which was not sufficiently effective, followed later by a second

Table 1
Description of the six cases treated with rituximab.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Sex	Female	Female	Male	Male	Female	Male
Age	54 years	68 years	53 years	42 years	54 years	47 years
Diagnosis of Graves' disease/of orbital relapse	March 2011	October 2012	November 2012	August 2011	August 2011	December 2012
Thyroidectomy	At 6 months	At 3 months	At 3 months	At 3 months	At 6 months	At 7 months
Tobacco	Yes	Non-smoker	Ex-smoker	Ex-smoker	Non-smoker	Non-smoker
Oculomotor disorders	Yes	Yes	Yes	Yes	Yes	Yes
NOSPECS	Very severe	Very severe	Very severe	Severe	Very severe	Severe
Visual field defects	Yes	Yes	Yes	Yes	Yes	Yes
Rituximab (time relative to diagnosis)	At 23 months	At 6 months	At 5 months	At 13 months	At 13 months	At 16 months
Rituximab (time relative to corticosteroids therapy)	13 months	1 month	0 month	6 months	6 months	6 months
Semi-urgent orbital decompression	At 13 months		At 5 months	At 8 months	At 7 months	
Coronal decompression (end of treatment)	At 30 months	At 8 months	At 24 months	At 15 months	At 17 months	At 23 months
Indication of treatment with rituximab	Decrease of visual acuity and visual field defect	Decrease of visual acuity and visual field defect	Decrease of visual acuity, visual field defect and corneal involvement	Visual field defect and inflammation	Decrease of visual acuity and visual field defect with compression of optical nerve on imaging	Visual field defect and inflammation

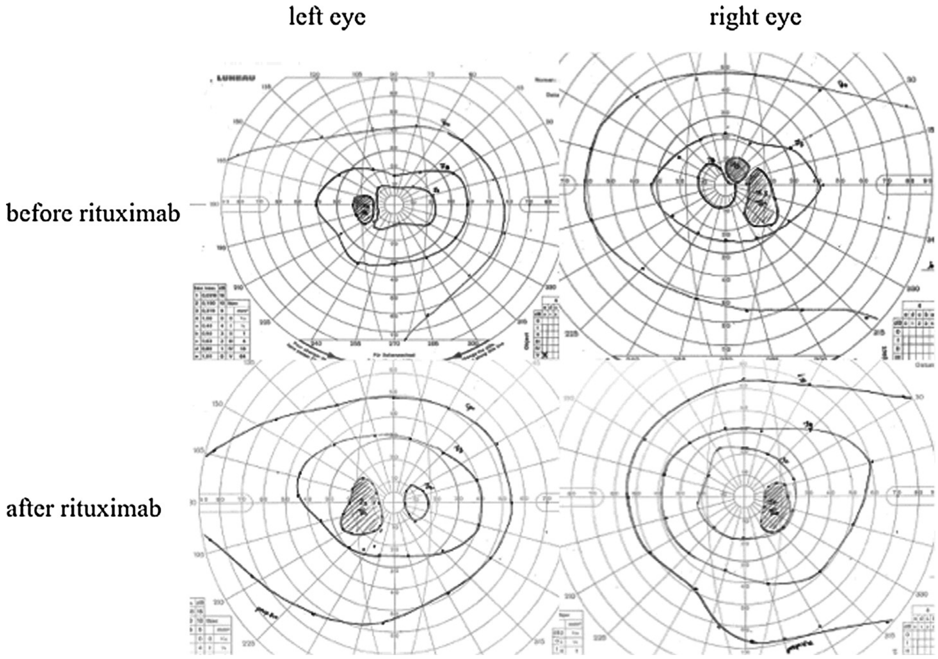

Fig. 2. Results of the Goldmann visual field before and three months after treatment with rituximab for case 3.

decompression surgery by the coronal approach. The other two patients did not have emergency orbital decompression surgery, but had orbital decompression surgery by the coronal approach at the end of treatment. Patients received Rituximab therapy zero to 13 months after completing corticosteroid therapy. No serious side effects or complications during rituximab therapy were observed (Table 1).

The indication was visual loss in four patients and/or modification of the visual field with the appearance of a central scotoma for at least one eye for all six patients, associated with optic nerve compression on imaging for one patient, severe damage to the corneal surface of one patient, and a persistently high inflammatory score for two patients, despite corticosteroid treatment.

Visual acuity improved in three of four cases and the visual field in four cases (Figs. 2 and 3). The inflammatory score was reduced in three cases. Proptosis decreased in three cases after treatment with rituximab and before orbital decompression by the coronal approach. Intraocular pressure decreased in all six cases.

For case 2, there was limited improvement of visual acuity and visual field after rituximab treatment and surgical orbital decompression. This result may be due to the panretinal

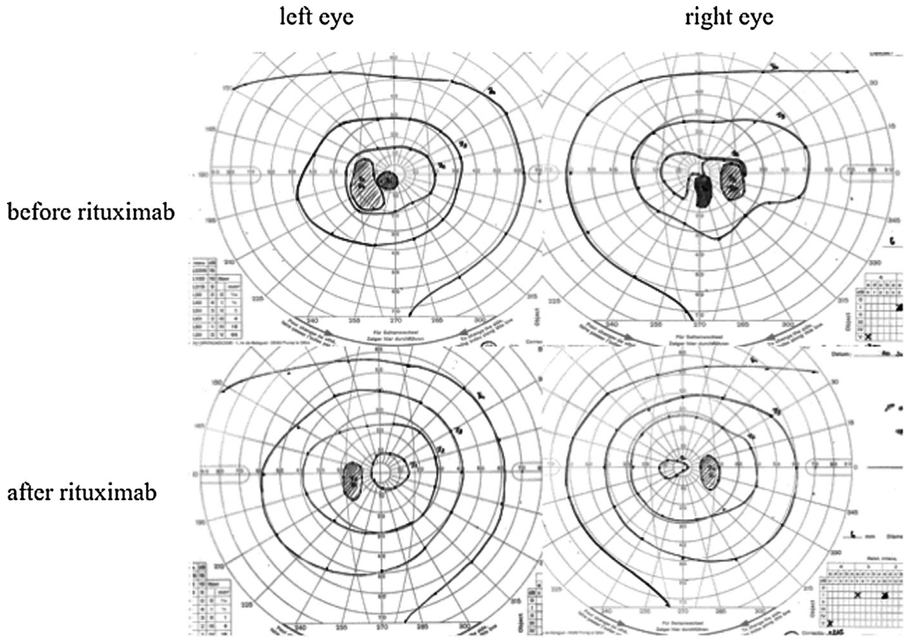

Fig. 3. Results of the Goldmann visual field before and three months after treatment with rituximab for case 6.

Table 2
Results of the treatment with rituximab on visual acuity, intraocular pressure, corneal lesions, orbital clinical inflammatory Mourits' score, proptosis, and Goldmann visual field.

	Visual acuity (decimal, Monoyer far scale and Parinaud near scale)		Intraocular pressure (mmHg)		Cornea		Mourits score (/7)	Proptosis (Hertel mm)		Goldmann visual field	
	Right eye	Left eye	Right eye	Left eye	Right eye	Left eye		Right eye	Left eye	Right eye	Left eye
Case 1											
One month before rituximab	2 P10	7 P2	22	26	Punctate keratitis	Punctate keratitis	3	20	20	Centrocaecal scotoma	Normal
Three to six months after rituximab	5 P10	7 P2	22	23	Normal	Punctate keratitis	3	19	18	Decrease of the scotoma	Normal
Last examination 33 months after treatment	4 P2	5 P2	15	14	Normal	Normal	1	20	20	Undefined	Undefined
Case 2											
One month before rituximab	5 P10	1,5 P14	26	25	Punctate keratitis	Punctate keratitis	3	21	20	Central scotomas	Central scotomas
Three to six months after rituximab	1,6 P8	5 P4	12	17	Punctate keratitis	Punctate keratitis	3	19	19	Central scotomas	Central scotomas
Last examination 23 months after treatment	1,6 P10	2 P10	13	14	Normal	Normal	3	17	17	Undefined	Undefined
Case 3											
One month before rituximab	Hand motion	1,6	20	20	Punctate keratitis	Punctate keratitis and Dellen effect	5	23	21	Central scotomas	Normal
Three to six months after rituximab	6 P2	6 P6	16	15	Normal	Normal	2	23	22	Disappearance of the scotoma	Normal
Last examination 24 months after treatment	12,5 P4	6,3 P2	17	15	Normal	Normal	1	17	18	Undefined	Undefined
Case 4											
One month before rituximab	10 P2	10 P2	23	23	Normal	Normal	3	22	20	Enlargement of the blind spot	Centrocaecal scotoma
Three to six months after rituximab	10 P2	10 P2	12	15	Normal	Normal	2	18	18	Normal	Normal
Case 5											
One month before rituximab	1,6 P10	Counting fingers	19	26	Punctate keratitis	Normal	1	18	19	Exclusion of the blind spot (I3)	Exclusion of the blind spot (I3)
Three to six months after rituximab	3 P8	0,5 P10	14	14	Punctate keratitis	Punctate keratitis	1	19	18	Central scotoma	Central scotoma
Last examination 39 months after treatment	6 P2	1,6 P10	14	14	Normal	Punctate keratitis	1	Undefined	Undefined	Undefined	Undefined
Case 6											
One month before rituximab	10 P2	10 P2	20	18	Punctate keratitis	Punctate keratitis	4	24	24	Exclusion of the blind spot and central reach	Exclusion of the blind spot and central reach
Three to six months after rituximab	10 P2	10 P2	17	17	Normal	Normal	2	25	25	Normal	Normal
Last examination 23 months after treatment	20 P2	16 P1,5	20	17	Normal	Normal	1	23	23	Undefined	Undefined

photocoagulation for diabetic retinopathy and diabetic cataract of the patient, which was aggravated by the corticosteroids (Table 2).

4. Discussion

Rituximab therapy was beneficial in second intention for the six patients in this study, based on three criteria, who had severe ophthalmopathy with inflammatory signs resistant to corticosteroids, decreased visual acuity and/or visual field defects.

Anti-CD20 treatments have made it possible to exploit the role of B cells in autoimmunity to treat a number of diseases.

B lymphocytes not only produce autoantibodies, but also activate CD4+ T cells, thus playing a role in inflammation. They are also important antigen presenting cells [15]. The CD20+ marker, the target of rituximab, is present during all stages of B cell maturation [16].

Several other non-validated treatment options are also being studied for the treatment of severe Graves' ophthalmopathy, such as cyclosporine [17] or anti-TNFα.

Rituximab has been used to treat non-Hodgkin lymphoma and autoimmune pathologies such as rheumatoid arthritis and cases of Graves' ophthalmopathies which are resistant to corticosteroid treatment.

It is generally well tolerated, but patients should be monitored for signs of intolerance or infection. This biotherapy must also be used with caution because of the resurgence of tuberculosis in developed countries [18].

Rituximab affects pro-inflammatory cytokine production and lymphocyte infiltration, but has no effect on the level of autoantibodies as demonstrated by Vannucchi et al. [19] and by El Fassi et al. [12].

Rituximab has been used to treat 43 patients for Graves' ophthalmopathies in uncontrolled studies resulting in inactivation of the inflammatory phase of the disease in 91% of cases, as reported in the literature up to 2014 [20]. Proptosis and diplopia also improved after treatment in most cases [20]. Proptosis decreased in three of our patients. However, all patients required muscle surgery, in agreement with the results of the series of Khanna et al. [10]. This level of efficiency has been demonstrated in long-term monitoring of a small group of patients [21].

A double-blind randomized study, published in 2014, comparing 31 patients treated with intravenous methylprednisolone or rituximab showed a significantly greater decrease of the inflammatory score in the rituximab group after 16 weeks of treatment. The patients exhibited improved oculomotor limitation and a reduction in the frequency of inflammatory relapses, but no significant improvement in proptosis [22]. The authors suggest that the use of lower doses of rituximab, 500 instead of 2000 mg, decrease the risk of complications, but have the same anti-inflammatory effect. Another study, that compared rituximab to a placebo, did not find a benefit for rituximab in reducing the inflammatory score [23]. However, the therapeutic window for intravenous corticosteroids was four weeks before rituximab therapy in this study, while it was three months for the previous one. This raises the question of the appropriate time to consider rituximab therapy in cases of corticosteroid resistance, when visual acuity and the visual field continue to deteriorate and the inflammatory score does not improve. In our series, this period was between 0 and 13 months. These last two published studies have the limitation that they did not examine the benefit of rituximab on optic neuropathy, which is a major problem and negatively affects the visual prognosis in severe ophthalmopathies. It has been effective on optic neuropathy in some cases [7,10,24], however, it is non-recommended in the last guidelines in 2016 because of the development of optic neuropathy after a rituximab treatment in some cases [6].

Rituximab has also been tested on relapsing Graves' disease of average severity, independently of any effects on the eyes, demonstrating an increase in TSH and a decrease in T4, up to 27 months after treatment. We have not been able to study this in our series as all patients underwent total thyroidectomy prior to rituximab therapy [25].

The positive results of our study must be balanced by the fact that four patients had initial emergency orbital decompression surgery (by collapse of the lateral and medial orbital walls) prior to rituximab therapy and all had final orbital decompression surgery by the coronal approach after rituximab therapy, during the follow-up period. Surgical removal of the lateral wall and collapse of the medial wall probably also helped to improve symptoms. However, surgery does not decrease lymphocyte infiltration of the orbit, in contrast to rituximab, as discussed by Salvi et al. [24]. We must also consider the fact that our patients received treatment by multiple intravenous injections of corticosteroids prior to being treated with rituximab, which prevents an assessment of the effectiveness of rituximab alone. However, Salvi et al. [22] have reported efficacy of rituximab to lower the inflammatory score when only 19% of the patients in their study received another prior anti-inflammatory treatment.

Rituximab suffers from the lack of a large controlled study against the standard treatment. The study of Salvi et al. [14,22] on 16 patients treated with rituximab versus 16 patients treated with corticosteroids reported superiority of rituximab for the inflammatory score and equivalence for proptosis. Validation of this result on larger cohorts, may lead more clinicians to use rituximab to treat severe inflammatory ophthalmopathies.

5. Conclusion

We successfully used rituximab to treat Graves' ophthalmopathies without significant side effects resulting in improvement of the symptoms of patients who responded inadequately to corticosteroids, however some patients had orbital decompression shortly before treatment by rituximab. We had positive results on patients with visual threat and optic neuropathy, combined or not with an initial surgical orbital decompression. The description of cases treated with rituximab in centers caring for patients with Graves' ophthalmopathies may allow a standardized management protocol for all European centers.

Disclosure of interest

The authors declare that they have no competing interest.

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Annales d'Endocrinologie 78 (2017) 27–32

Annales d'Endocrinologie
Annals of Endocrinology

Original article

Overdiagnosis of thyroid cancer in the Marne and Ardennes Departments of France from 1975 to 2014

Évaluation du surdiagnostic du cancer de la thyroïde dans les départements de la Marne et des Ardennes de 1975 à 2014

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Abstract

Objectives. – Incidence of thyroid cancer has increased considerably in France in recent years, but the mortality rate has declined only slightly. Part of this increased incidence could be attributable to overdiagnosis. We aimed to estimate the contribution of overdiagnosis to the incidence of papillary thyroid cancer. *Material and methods.* – Incidence rates were calculated based on data from the specialised Marnes-Ardennes thyroid cancer registry, for cancers diagnosed between 1975 and 2014, by age category and by five-year period. The population was divided into two groups according to pTNM classification at diagnosis (i.e. localised or invasive). Overdiagnosis was defined as the difference in incidence rates between the invasive cancer and localised cancer groups. This rate was then divided by the incidence rate in the localised cancer group for the most recent period (2010–2014) to obtain the proportion of cancers attributable to overdiagnosis. *Results.* – In total, 2008 patients were included. The proportion of incidence attributable to overdiagnosis for the period 2010–2014 was estimated at 7 and 62% in men and women aged < 50 years respectively, and at 65 and 73% respectively in men and women aged ≥ 50 years. *Conclusion.* – We observed a high proportion of cancers attributable to overdiagnosis. This finding raises the issue of patient management, with the risk of overtreatment, and the repercussions on quality of life for patients diagnosed with cancer.
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Keywords: Thyroid neoplasms; Thyroid gland; Incidence; Overdiagnosis

Résumé

Objectif. – L'incidence du cancer de la thyroïde a beaucoup augmenté en France, pourtant le taux de mortalité n'a que très faiblement diminué. La possibilité d'un surdiagnostic est souvent évoquée. L'objectif de notre étude était d'estimer la part de surdiagnostic dans l'incidence du cancer de la thyroïde de type papillaire. *Matériels et méthodes.* – Les taux d'incidences (TI) ont été calculés à partir des données du « Registre spécialisé du cancer de la thyroïde Marne-Ardennes » diagnostiqué entre 1975 et 2014, par tranches d'âge et par périodes quinquennales. La population a été séparée en 2 groupes définis par la classification pTNM au diagnostic (« cancer localisé » et « cancer étendu »). Le surdiagnostic a été défini par la différence entre l'évolution du TI dans le groupe « cancer étendu » et dans le groupe « cancer localisé ». En divisant ce taux par le TI du groupe « localisé » de la dernière période (2010–2014), un pourcentage estimant la part de surdiagnostic a été obtenu. *Résultats.* – Notre étude a porté sur 2008 patients. Les parts de l'incidence attribuables au surdiagnostic, pour la période 2010–2014, ont été estimées chez les hommes et les femmes de moins de 50 ans à 7 et 62 %, respectivement. Les estimations chez les hommes et les femmes de plus de 50 ans étaient de 65 % et 73 %, respectivement.

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http://dx.doi.org/10.1016/j.ando.2016.07.005
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Conclusion. – Les taux attribuables au surdiagnostic retrouvés dans notre étude sont importants. Se posent alors les problèmes de la prise en charge du patient avec les risques de surtraitement et des conséquences sur la qualité de vie de l'annonce du diagnostic de ce type de cancer.

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Mots clés : Néoplasmes thyroïdiens ; Glande thyroïdienne ; Incidence ; Surdiagnostic

1. Introduction

The incidence of thyroid cancer has been increasing for several decades [1,2]. In France, in 1980, the incidence rate per 100,000 inhabitants was 1.0 in men and 2.9 in women [3]. By 2012, this rate had risen to 5.5 in men and 13.8 in women [4]. This increase is mainly driven by an increase in the number of papillary cancers, and particularly, small tumours (< 20 mm) [2,5]. Several authors have proposed possible explanations for this phenomenon [5,6], and progress in diagnostic techniques is regularly cited [7,8]. However, although there has been a substantial increase in the rate of thyroid cancer in France, the mortality rate has only slightly declined, from 0.4 in men and 0.6 in women in 1980, to 0.2 in both men and women in 2012 [4], and the mortality rate has even remained stable in the USA [6].

These circumstances suggest the likelihood that part of this increase in incidence is due to overdiagnosis. Overdiagnosis is defined as the diagnosis of disease that would otherwise not go on to cause symptoms or death [9], and this phenomenon has already been studied in the context of breast and prostate cancer [9,10]. To the best of our knowledge, the impact of overdiagnosis on thyroid cancer incidence has never been studied in France.

Therefore, we aimed to estimate the proportion of the increase in differentiated papillary thyroid cancer incidence that could be attributed to overdiagnosis in the Marne and Ardennes Departments of France between 1975 and 2014 using data from the Marne-Ardennes thyroid cancer registry.

2. Subjects and methods

2.1. Study design

Observational, descriptive, longitudinal, historical cohort study using data from the specialised thyroid cancer registry of the Marne-Ardennes Departments in France.

2.2. Study population

We included all subjects living in the Marne or Ardennes Departments of France and who were diagnosed with papillary thyroid cancer between 1975 and 2014. We excluded patients in whom cancer stage was not determined.

2.3. Variables recorded

We recorded socio-demographic variables, i.e. age at diagnosis and sex. Cancer characteristics were also recorded, namely year of diagnosis, International Classification of Diseases (ICD) 10th revision code [11] associated with the papillary cancer, and the pTNM 2002 status [12]. Patients with cancers classed as ICD codes 8260, 8340, 8341, 8342, 8343, 8344, 8350 were included.

Cancer stage was defined using the pTNM classification at diagnosis, and based on this classification, patients were divided into two groups according to the size of the tumour, the extent of spread beyond the thyroid, lymph node involvement, and presence of metastasis at diagnosis. The "localised cancer" group comprised patients with cancers classified as pT1 or pT2, pN0 or Nx, or M0. The "invasive cancer" group comprised patients with cancer classified as stage pT3 or pT4 and/or pN1 or M1.

2.4. Statistical analysis

Quantitative variables are described as mean ± standard deviation (SD) or median, and qualitative variables as number (percentage).

2.4.1. Incidence rate for papillary thyroid cancers

All calculations of incidence rates were stratified by sex. Incidence rates were calculated per 100,000 person-years (PY), by 5-year age groups (0–4 years, 5–9 years, 10–14 years etc) and by 5-year periods (1975–1979, 1980–1984, 1985–1989, 1990–1994, 1995–1999, 2000–2004, 2005–2009, 2010–2014). The numerator was the number of newly diagnosed cases of papillary cancer, and the denominator was the population of the Marne and Ardennes Departments, by age category and by 5-year period, and by sex (population data from the National Institute of Statistics and Economic Studies, France [13]). The number of person-years was calculated as the sum of the population on 1st January of each of the 5 years (for example, for women for 1975–1979, the number of person-years was the number of women on 1st January 1975 + on 1st January 1976 + on 1st January 1977 + on 1st January 1978 + on 1st January 1979). Direct age standardization was performed using the world population as reference [14,15].

2.4.2. Incidence rate of overdiagnosis

All overdiagnosis analyses were stratified by age and sex. The population was divided into two age groups, namely above and below the median age at diagnosis of the study population.

Overdiagnosis is defined as the diagnosis of disease that would otherwise not go on to cause symptoms or death, and was calculated by comparing the incidence rate of the localised cancer group and that of the invasive cancer group, according to the methodology used in a recent study [16].

In view of the increase in the incidence rate (IR) of thyroid cancer since 1975, the IR for the most recent

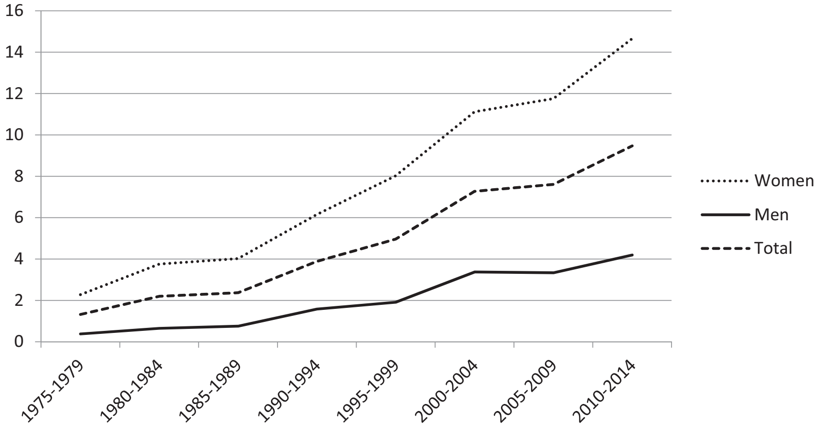

Fig. 1. Incidence rates of papillary thyroid cancer standardised in the world population, in men, women and the overall population, per 100,000 and per 5-year period (Thyroid Cancer Registry of the Marne-Ardennes Departments, France).

period (2010–2014) was compared to that of the first period for which data were available (1975–1979) for each group ($\mathrm{IR}^{+}_{\mathrm{invasive}} = \mathrm{IR}_{2010\text{–}2014(\mathrm{invasive})} - \mathrm{IR}_{1975\text{–}1979(\mathrm{invasive})}$ and $\mathrm{IR}^{+}_{\mathrm{localised}} = \mathrm{IR}_{2010\text{–}2014(\mathrm{localised})} - \mathrm{IR}_{1975\text{–}1979(\mathrm{localised})}$).

We considered $\mathrm{IR}^{+}_{\mathrm{invasive}}$ to represent the true natural course of thyroid cancer. IR attributable to overdiagnosis was calculated by subtracting the increase in the invasive group from the increase in the localised group ($\mathrm{IR}_{\mathrm{overdiagnosis}} = \mathrm{IR}^{+}_{\mathrm{localised}} - \mathrm{IR}^{+}_{\mathrm{invasive}}$). By dividing this adjusted rate by the IR for the localised cancer group for the most recent period, we obtained a percentage estimating the proportion attributable to overdiagnosis ($(\mathrm{IR}_{\mathrm{overdiagnosis}}/\mathrm{IR}_{2010\text{–}2014(\mathrm{localised})})*100$ [16,17].

All analyses were performed using SAS version 8.2 (SAS Institute Inc., Cary, NC, USA).

3. Results

In total, 2009 patients were included in this study, but one was subsequently excluded for lack of surgery (tumour size unknown, N0 and M0, thus impossible to classify). Our final analysis included 2008 patients; 1589 (79%) were women; average age was 48 ± 15 years, with a median age of 49 years. The two age groups were thus < 59 and ≥ 50 years.

Overall, 1695 (84%) of patients were stage pT1 or pT2 and 313 (15%) were pT3 and pT4; 437 (22%) were N1, and 40 (2%) were M1. The localised cancer group comprised 1423 patients (71%), and the invasive cancer group comprised 585 (29%).

The changes in age-standardised incidence rates per 100,000 in men and women, by 5-year period, are shown in Fig. 1. The changes in age-standardised incidence rates per 100,000 in localised cancer and invasive cancer, by 5-year period, are shown in Fig. 2. The standardised incidence rate for localised cancer increased by 6.30 cases per 100,000 PY between the 1975–1979 period and the 2010–2014 period. The standardised incidence rate for invasive cancer increased by 1.87 cases per 100,000 PY between the 1975–1979 period and the 2010–2014 period. The increase in incidence in invasive thyroid cancer over time were non significant but it does not decrease. Standardized incidence rates per 100,000 by 5-year period for men and women aged < 50 years are shown in Table 1.

The standardised incidence rate for women aged < 50 years increased by 5.78 cases per 100,000 PY in the localised cancer group, and by 1.58 cases per 100,000 PY in the invasive cancer group between the 1975–1979 period and the 2010–2014 period. The rate attributable to overdiagnosis was estimated at 4.20 cases per 100,000 PY. When divided by the incidence rate of the most recent period (6.75 for the period 2010–2014), the proportion of cases attributable to overdiagnosis was 62% (Table 2).

The standardised incidence rate for men aged < 50 years increased by 0.96 cases per 100,000 PY in the localised cancer group, and by 0.89 cases per 100,000 PY in the invasive cancer group between 1975–1979 and 2010–2014. The rate attributable to overdiagnosis was estimated at 0.07 cases per 100,000 PY. When divided by the incidence rate of the most recent period (1.05 for 2010–2014), the proportion of overdiagnosis was thus 7% (Table 2).

Standardised incidence rates per 100,000 by 5-year period for men and women aged 50 years and over are shown in Table 3.

The standardised incidence rate for women aged ≥ 50 years increased by 4.24 cases per 100,000 PY in the localised cancer group, and by 0.79 cases per 100,000 PY in the invasive cancer

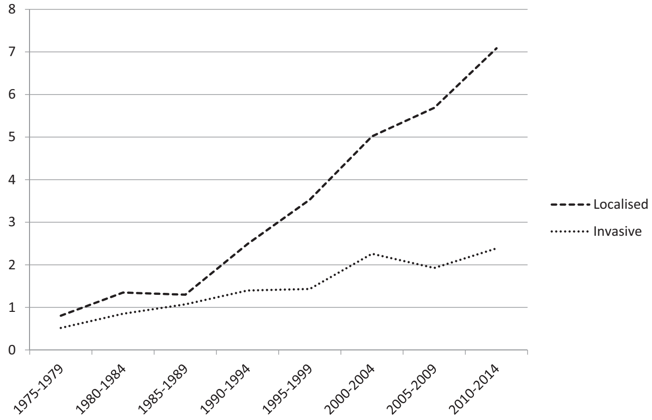

Fig. 2. Incidence rates of papillary thyroid cancer standardised in the world population, in the localised cancer and invasive cancer groups, per 100,000 and per 5-year period (Thyroid Cancer Registry of the Marne-Ardennes Departments, France).

Table 1
Standardised incidence rates per 100,000 persons for papillary thyroid cancer in women and men aged less than 50 years.

5-year period	Women < 50 years		Men < 50 years	
	Localised cancer	Invasive cancer	Localised cancer	Invasive cancer
1975–1979	0.97	0.59	0.09	0.18
1980–1984	1.85	0.75	0.05	0.25
1985–1989	1.83	1.24	0.17	0.27
1990–1994	2.71	1.41	0.43	0.63
1995–1999	3.63	1.61	0.75	0.35
2000–2004	3.80	2.25	0.94	0.78
2005–2009	4.01	1.89	0.73	0.66
2010–2014	6.75	2.17	1.05	1.07

Table 2
Proportion of incidence attributable to overdiagnosis for the period 2010–2014 in women and men, by age group.

	2010–2014
Women < 50 years	
Overdiagnosis rate (per 100,000)	4.20
Percentage overdiagnosis (%)	62
Women ≥ 50 years	
Overdiagnosis rate (per 100,000)	3.45
Percentage overdiagnosis (%)	73
Men < 50 years	
Overdiagnosis rate (per 100,000)	0.07
Percentage overdiagnosis (%)	7
Men ≥ 50 years	
Overdiagnosis rate (per 100,000)	1.00
Percentage overdiagnosis (%)	65

group between the 1975–1979 period and the 2010–2014 period. The rate attributable to overdiagnosis was estimated at 3.45 cases per 100,000 PY. When divided by the incidence rate of the most recent period (4.74 for the period 2010–2014), the proportion of cases attributable to overdiagnosis was 73% (Table 2).

The standardised incidence rate for men aged ≥ 50 years increased by 1.48 cases per 100,000 PY in the localised cancer group, and by 0.48 cases per 100,000 PY in the invasive cancer group between 1975–1979 and 2010–2014. The rate attributable to overdiagnosis was estimated at 1.00 cases per 100,000 PY. When divided by the incidence rate of the most recent period (1.54 for 2010–2014), the proportion of overdiagnosis was thus 65% (Table 2).

Table 3
Standardised incidence rates per 100,000 persons for papillary thyroid cancer in women and men aged 50 years and over.

5-year period	Women ≥ 50 years		Men ≥ 50 years	
	Localised cancer	Invasive cancer	Localised cancer	Invasive cancer
1975–1979	0.50	0.21	0.06	0.05
1980–1984	0.77	0.39	0.04	0.31
1985–1989	0.49	0.46	0.14	0.18
1990–1994	1.60	0.44	0.21	0.32
1995–1999	2.18	0.61	0.51	0.30
2000–2004	4.00	1.07	1.21	0.44
2005–2009	5.04	0.82	1.49	0.45
2010–2014	4.74	1.00	1.54	0.53

4. Discussion

To the best of our knowledge, this is the first study to investigate the proportion of papillary thyroid cancer cases attributable to overdiagnosis in France. The findings are based on registry data, thus ensuring absence of selection bias, and guaranteeing the exhaustiveness of the data across two French Departments over a long period (40 years). Our study shows that there is a substantial proportion of overdiagnosis of papillary thyroid cancer among women aged > 50 years (73%) and < 50 years (62%) as well as in men (73%), in women aged < 50 years (62%) as well as in men aged over 50 (65%). The rate of overdiagnosis was much lower in men younger than 50 years of age, at only 7%.

The changes in incidence rates for papillary thyroid cancer in this study are in the line with previous reports in the literature [1,2]. Our findings are similar to those of the study by O'Grady et al. in 2015 in the USA [16]. After age-standardisation on the American population, the proportion of thyroid cancers attributable to overdiagnosis was 45.5% in women aged < 50 years, 60% in women over 50, and 41% in men aged 50 years and over. As in our study, the proportion of overdiagnosis was also much lower in men aged < 50 years, at only 5.5%. However, comparison of these two studies presents certain limits, in that they were not age-standardised on the same population. In addition, O'Grady's study excluded patients aged under 20, and their classification was somewhat different to ours (i.e. localised cancers measuring more than 4 cm were included in the localised group in O'Grady's study, whereas they were classed in the invasive group in our study).

We chose not to divide our population into two groups based on TNM staging. Indeed, localised tumours measuring more than 4 cm (and diagnosed clinically by palpation), as well as tumours extending beyond the thyroid capsule, or N1, were not included in the "localised cancer" group in our study. These types of tumours were not considered as attributable to overdiagnosis.

There are several possible explanations for the increase in overdiagnosis [18]. The most likely contributing factors are the advent of echography around 1985, and the progress made in diagnostic techniques (cytology under echographic guidance, hormonal measurements) [19]. In addition, pathology slices of thyroidectomy specimens are ever thinner, leading to diagnosis of very small cancers (at the scale of a millimetre) that had gone undiagnosed before a surgery performed for benign indications (such as goitre or hyperthyroidism). The frequency of millimetre-sized thyroid cancers is estimated at around 36% in the general population [20], thus providing a large reservoir of latent disease.

In our study, the difference in incidence rates attributable to overdiagnosis between men and women aged below 50 years was quite substantial, with proportions of 0.07 and 4.19 per 100,000 respectively. The female/male ratio was high (sex ratio 3.8).

Indeed, thyroid disorders, and particularly thyroid cancer, are more frequent in women than in men, with a sex ratio in France ranging from 3.4 to 4.3 [2]. Women also have more frequent medical check-ups (for pregnancy, for example [21] or prescription of oral contraceptives in women aged < 50). The average age of our study population was 48 years, with a median of 49 years, a finding similar to that of other studies from the USA [16], and Australia [22]. It is also established that consumption of healthcare resources increases with age [23], which could explain the difference in the proportion of cases attributable to overdiagnosis between men younger than vs older than 50 years.

While the Tchernobyl accident of 1986 did not have any direct consequences on the level of irradiation in France, it did lead to heightened awareness of thyroid disease among the general population and physicians [24,25].

Among the thyroid cancer cases diagnosed, many would never have progressed and can thus be considered as overdiagnosis. Others were diagnosed when the cancer was localised, corresponding to early-stage disease. The repercussions on incidence rates of these early-stage diagnoses should lead to a subsequent rise in localised cancers, and a reduction in invasive disease. However, we did not observe any such decrease in our study, thus supporting our hypothesis of overdiagnosis.

The risk inherent to overdiagnosis is that patients will be overtreated [9]. Some authors advocate active surveillance or conservative management for very small sized cancers and this approach is currently being investigated [26].

The small number of cases may lead to less precise estimation in incidence rates. A larger study at a national level is warranted to confirm our findings. Nonetheless, this is the first study to date performed on data from France, and the only study to be age-standardised on the world population. This should allow comparison with other studies.

In conclusion, the observed increase in papillary thyroid cancer incidence rates is largely attributable to overdiagnosis. As for other organs, notably the prostate, the prerequisites for thyroid cancer overdiagnosis to occur are a large reservoir of latent disease, and increased diagnostic activity. The consequences of overdiagnosis include overtreatment, which not only generates additional healthcare expenditure, but also has an impact on patients' quality of life when they are diagnosed with cancer. While we cannot ignore these diagnoses, it is important to recognize potential overdiagnosis and avoid overtreatment, by adhering to recommendations for management issued by professional societies.

Disclosure of interest

The authors declare that they have no competing interest.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

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Annales d'Endocrinologie
Annals of Endocrinology

Annales d'Endocrinologie 78 (2017) 33–37

Original article

Change in women's eating habits during the menstrual cycle

Modification du comportement alimentaire de la femme au cours du cycle menstruel

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Abstract

Objectives. – During the menstrual cycle, the influence of hormonal variations on dietary habits in women has been suggested by several studies. In this context, our work aimed to assess the spontaneous food intake and the anthropometric parameters of women at different periods of their menstrual cycles. *Methods.* – This prospective study included 30 healthy women with regular periods (28 to 30 days), aged between 18 and 45. We assessed the spontaneous food intake and the anthropometric measurements (weight and waist circumference) of the participants, during the follicular, peri-ovulatory and luteal phases of their menstrual cycles. *Results.* – Our results showed a slight but significant increase in body weight during the luteal phase ($P = 0.022$) and the follicular phase ($P = 0.017$) compared with the peri-ovulatory phase, without any significant change in waist circumference. The caloric intake increased during the peri-ovulatory ($P < 0.001$) and the luteal phases ($P < 0.001$), compared with the follicular phase, with a significant increase in carbohydrate ($P < 0.001$), lipid ($P = 0.008$) and protein ($P = 0.008$) intake. *Conclusions.* – Our study showed a significant decrease in women's weight during the peri-ovulatory phase, with a significant increase in caloric intake during the luteal phase of the menstrual cycle. Divergent results have been reported by other authors and the physiopathology of these changes is still poorly understood.
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Keywords: Eating habits; Weight; Menstrual cycle; Women

Résumé

Objectifs. – L'influence des variations hormonales durant le cycle menstruel sur le comportement alimentaire des femmes a été suggérée par plusieurs études. Les objectifs de notre étude étaient d'évaluer et de comparer l'apport alimentaire spontané ainsi que les paramètres anthropométriques des femmes durant les différentes phases de leurs cycles menstruels. *Méthodes.* – Étude prospective concernant 30 femmes bien portantes, bien réglées (cycles menstruels réguliers de 28 à 30 jours), âgées de 18 à 45 ans. Nous avons évalué l'apport alimentaire spontané, le poids et le tour de taille de ces participantes durant les 3 phases d'un même cycle menstruel (phase folliculaire, péri-ovulatoire et lutéale). *Résultats.* – Nous avons noté une augmentation modérée mais significative du poids durant la phase lutéale ($p = 0{,}022$) et la phase folliculaire ($p = 0{,}017$) par rapport à la phase péri-ovulatoire, sans variation significative du tour de taille. L'apport alimentaire spontané augmentait durant les phases péri-ovulatoire ($p < 0{,}001$) et lutéale ($p < 0{,}001$) en comparaison de la phase folliculaire, avec une augmentation significative des apports en glucides ($p < 0{,}001$), en lipides ($p = 0{,}008$) et en protides ($p = 0{,}008$). *Conclusions.* – Notre étude a montré une diminution significative du poids durant la phase péri-ovulatoire, avec augmentation des apports alimentaires pendant la phase lutéale du cycle menstruel chez les femmes. Des résultats divergents ont été rapportés par d'autres auteurs. La physiologie des liens entre le cycle menstruel et l'alimentation de la femme est encore mal élucidée.
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Mots clés : Habitudes alimentaires ; Poids ; Cycle menstruel ; Femme

1. Introduction

Food intake is influenced by neurochemical, hormonal, physiological and psychological factors. Several studies have shown significant variations in appetite and in energy intake in women during their menstrual cycles [1–4].

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http://dx.doi.org/10.1016/j.ando.2016.07.001
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These variations are in part explained by the influence of estrogen and progesterone on gastric emptying and on the secretion of some gastrointestinal hormones such as glucagon-like-peptide-1 (GLP-1) and cholecystokinin (CCK), which are important factors for the regulation of appetite and energy intake [1]. In this context, we conducted this prospective study, whose objectives were:

- to evaluate spontaneous food intake by women during the follicular, the peri-ovulatory and the luteal phase of their menstrual cycles;
- to compare women's intake of food as well as their weight and waist circumference during the three phases of their menstrual cycles.

2. Subjects and methods

It was a prospective study that included 30 healthy women. All the participants had given their informed consent to participate in the study.

2.1. Inclusion criteria

- Age between 18 and 45 years old;
- regular periods (28 to 30 days).

2.2. Exclusion criteria

- Women on hormonal contraception or corticosteroid treatment;
- pregnant or lactating women;
- a personal history of serious diseases that may affect eating habits: neoplasia, neurological impairment, anorexia nervosa, renal, hepatic, respiratory or cardiac diseases;
- a personal history of endocrine or metabolic diseases.

2.3. Study design

Each woman included in the study was followed for a whole menstrual cycle (28 to 30 days), using a pre-established form. Three visits were planned for each participant:

- first visit: in the early follicular phase (between day 1 and day 3 of the menstrual cycle);
- second visit: in the ovulatory phase (between day 12 and day 16);
- third visit: in the late luteal phase (premenstrual period = 1–3 days before anticipated menstruation, based on self-reported historical cycle data).

On each visit, the participants had:

- a dietary survey: recorded by a qualified dietician, in order to estimate the total caloric intake and the distribution of macronutrients (carbohydrates, lipids, proteins). Photos of plate were used to achieve food investigation;
- a measurement of their anthropometric parameters (weight and waist circumference). The waist circumference was measured (in cm), using a measuring tape, midway between the iliac crests and the last costal margin.

2.4. Data analysis

Data analysis was performed using the following software:

- Bilnut 3: for the dietary surveys (to calculate the total energy intake, carbohydrate, protein and lipid intake on each visit);
- SPSS version 11.5: for statistical analysis. The numerical results are given as mean ± standard deviation and the qualitative results as percentages. The comparative statistical analysis used:
  - ○ the Student's *t*-test for continuous variables, and in case of low number, the nonparametric Mann-Whitney test,
  - ○ the Chi^2 test for discontinuous variables and in case of non validity of this test (and comparison of 2%), the Fisher bilateral exact test.

P-values lower than 0.05 were considered as statistically significant.

3. Results

3.1. General characteristics of the participants

Our study included 30 participants: 23 unmarried (76.7%) and 7 married women (23.3%). Their ages varied from 18 to 43 (mean age: 27.1 ± 7.8 years).

The age of menarche varied between 11 and 14 years with a mean age of 12.4 ± 0.9 years.

3.2. Changes in anthropometric measurements during the menstrual cycle

The initial body mass index of our participants in the follicular phase was 25.6 ± 5.2 kg/m^2 (20.3–32.8 kg/m^2).

The average weight was significantly higher during the late luteal phase ($P = 0.022$) and at the follicular phase of the menstrual cycle ($P = 0.017$) than in the peri-ovulatory phase (Fig. 1).

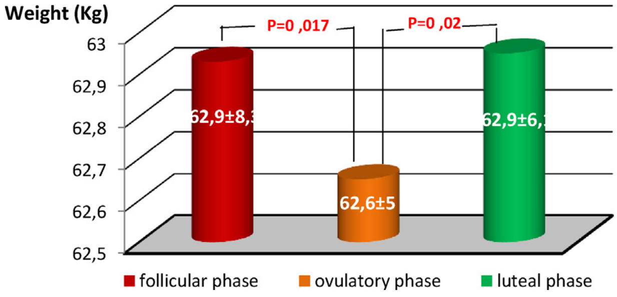

Fig. 1. Weight changes during the menstrual cycle.

Table 1
Involvement of each macronutrient in total caloric intake increasing between follicular, ovulatory and luteal phases.

	Follicular vs ovulatory phase			Follicular vs luteal phase		
Macronutrients	Carbohydrates	Fat	Protein	Carbohydrates	Fat	Protein
Involvement in total caloric intake increasing (%)	56	36	8	59	34	7

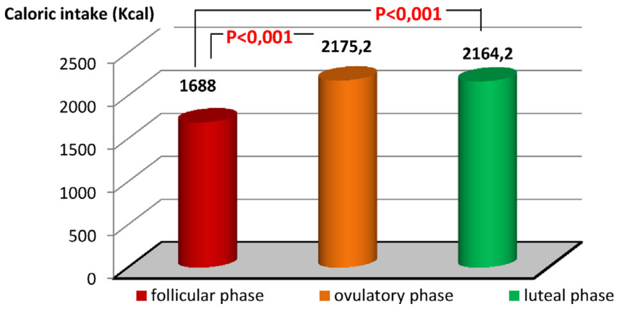

Fig. 2. Total caloric intake changes during the menstrual cycle.

However, the mean waist circumference remained unchanged during the menstrual cycle: 77.6 ± 8.8 cm in the follicular phase, 77.6 ± 9.2 cm in the peri-ovulatory phase and 78.3 ± 9.5 cm in the luteal phase ($P = \mathrm{NS}$).

3.3. Dietary survey data

Total caloric intake varied during the menstrual cycle (Fig. 2). It was significantly higher during the peri-ovulatory (2175.2 ± 321.8 Kcal/day) and luteal phases (2164.2 ± 290.3 Kcal/day) than in the follicular one (1688 ± 332 Kcal/day). This additional food intake interested carbohydrates as well as lipids and proteins. Thus, the carbohydrate intake increased significantly in the peri-ovulatory phase (315.7 ± 30.9 g/day vs 246.4 ± 26.8 g/day; $P < 0.001$) and in the luteal phase (309.5 ± 34.3 g/day vs 246.4 ± 26.8 g/day; $P = 0.002$) compared to the follicular phase (Fig. 3). We also found a significant increase in fat and protein intake in the peri-ovulatory phase ($P = 0.008$ for each one, Fig. 3).

However, the additional food intake was more important for carbohydrates: 56% of total caloric intake increase in peri-ovulatory phase compared to follicular phase, and 53% of this increase in luteal phase compared to follicular phase were linked to carbohydrates intake (Table 1).

4. Discussion

Our study showed a significant increase in body weight during the luteal and the follicular phases, with a significant increase in caloric intake during the peri-ovulatory and the luteal phases of the menstrual cycle. Despite our small sample, our pilot study concerned healthy women in the general population. Our findings provide a basis on which we can rely to carry larger multicenter studies to better understand the relationship between food intake and menstrual cycle in women.

However, our study has some limitations. There was no measurement of fat and lean masses. On the other hand, there was no assessment of steroid's plasmatic levels to be sure about the phase of the menstrual cycle. But all our participants had regular menses between 28 and 30 days.

We found a significant increase in women's weight during the late luteal phase ($P = 0.022$) and the early follicular phase ($P = 0.017$) compared to the peri-ovulatory phase. Our results are consistent with those reported by previous authors [2] who suggest that excessive consumption of carbohydrates is the cause of weight gain in some women during the premenstrual period.

However, we did not find a significant variation in waist circumference during the different phases of the menstrual cycle. This parameter has not been studied by other authors. It seems that abdominal fat is not the factor that explains women's weight variations during their menstrual cycles.

In our study, the total caloric intake was significantly higher during the peri-ovulatory and luteal phases ($P < 0.001$ for each

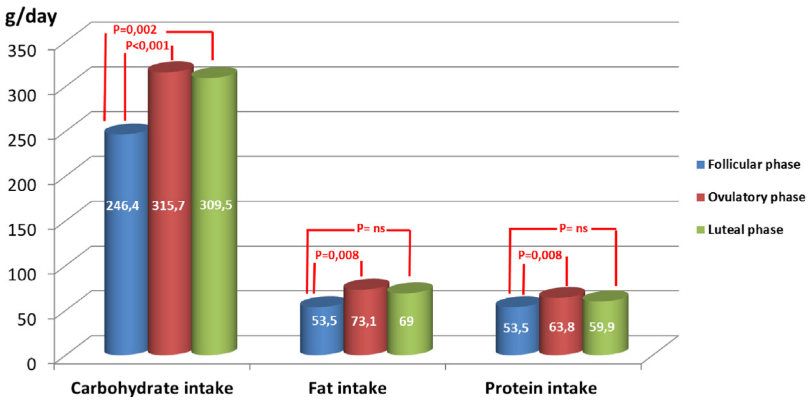

Fig. 3. Carbohydrate, fat and protein intake variation during the menstrual cycle.

one) than in the follicular phase and it was especially a carbohydrate intake's increase.

In fact, a cyclic variation of energy and macronutrient intake has been reported by several previous studies which showed that the most important changes were usually observed just before menstruation (late luteal phase) [2,5–7], with an increase in caloric intake of about 150 kcal per day in this period [5,6,8]. In the study by Tucci et al., the participants ingested approximately 15% more calories in the luteal phase [5]. It is important to note that, in this study, the eaten food was not composed of real meals but of snacks. This finding has implications on weight control [9]. The study of Bryant [10] showed that women consume about 100 kcal/day higher in the premenstrual phase compared to the rest of the cycle. According to these authors, a sustained supply of this amount of energy would result in a gain of approximately 5 kg of body weight over 12 months (assuming all other variables are constant) [10].

Similarly, the study by Pliner and Fleming showed that weight and food consumption were significantly higher during the luteal phase than during the follicular phase [11].

There are often dietary compulsions during this period of the cycle, especially for sweet foods and chocolate. According to Hormes and Rozin, the taste for chocolate is specifically related to the luteal phase in the menstrual cycle [12].

This could be explained by the change in ovarian hormones levels during the menstrual cycle. During the luteal phase, when both estrogen and progesterone increase, food intake increases, specifically sweet foods; in the follicular phase, with only increased oestrogen levels, food intake seems to decrease [2,13–17].

In addition, fluctuations in appetite, cravings and energy intake during the menstrual cycle may occur in parallel with cyclical rhythms in serotonin, which can be accompanied by affective symptoms like depression [18].

Our study showed a weight loss of 300 g during ovulation period in front of an increase food intake of 500 Kcal. This suggests that the daily energy expenditure may increase in the luteal [19]. However, this increment vary from one study to another, with important inter- and intraindividual variation. Thus, the simultaneous increase in the energy intake and energy expenditure can lead to a random variation of the weight. Also, this variation of 300 g may be often present many times within the menstrual cycle, but we do not have daily weight assessment in our work.

Analysis of the dietary surveys in our study showed a significant increase in fat and protein intake during the peri-ovulatory and late luteal phases compared to the follicular period. The significance of these results have been debated in the literature.

In 1989, Lyons revealed a significant decrease in protein intake during the ovulatory phase [20]. Also, in 2012, McNeil and Doucet [21] showed a decrease in the luteal phase. On the other hand, the study by Tarasuk and Beaton in 1991 showed an increase during the premenstrual phase [7].

Several studies have shown that fat intake tends to increase more during the premenstrual phase than in the rest of the cycle [17,18].

5. Conclusion

Our study showed a significant decrease in women's weight during the peri-ovulatory phase, without any significant difference in waist circumference.

It also showed that there is a change in dietary habits during the menstrual cycle, with an increase in total caloric intake, carbohydrate, protein and fat intake in the peri-ovulatory and luteal phases. Thus, changes in dietary habits during the menstrual cycle should be taken into consideration in the interpretation of dietary evaluation in women.

The relationship between food intake and hormonal fluctuations during the menstrual cycle is very complex and involves several regulatory systems. The exact mechanisms are still poorly understood and require further investigations.

Disclosure of interest

The authors declare that they have no competing interest.

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Annales
d'Endocrinologie
Annals of Endocrinology

Annales d'Endocrinologie 78 (2017) 38–42

Review

PET imaging for thyroid cancers: Current status and future directions

Imagerie TEP dans les cancers thyroïdiens : position actuelle et perspectives

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Abstract

Positron emission tomography–computed tomography (PET/CT) combines both functional and anatomic information and provides in vivo molecular information on biological processes that can be useful at different steps of evolution of thyroid cancers. ^{18}Fluorodeoxyglucose being highly trapped in rapidly dividing cells makes ^{18}F-FDG-PET recommended in the staging, prognostic evaluation and follow-up of metastatic and/or of poorly differentiated thyroid carcinomas. ^{18}F-FDG PET/CT can help in the localization of persistent/recurrent disease. However, its sensitivity depends widely on tumor burden and histology. Iodine 124 (^{124}I) is currently under evaluation for diagnosis and pretherapeutic dosimetry planning. PET/CT using ^{18}F-FDOPA is the most sensitive radiopharmaceutical for localizing persistent/recurrent medullary thyroid carcinoma (MTC). However, its sensitivity depends on calcitonin levels, with a threshold value of around 150 pg/mL. ^{18}F-FDG PET/CT can also be used in MTC with short calcitonin or CEA doubling time.
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Keywords: Thyroid carcinoma; FDG-PET; Iodine-124; FDOPA

Résumé

La tomographie par émission de positons couplée à la TDM (TEP-TDM) est une imagerie fonctionnelle avec support anatomique pouvant être utilisée aux différents temps de la prise en charge des cancers thyroïdiens. Le ^{18}Fluorodeoxyglucose (^{18}F-FDG) est capté en grande quantité par les cellules en division rapide. La TEP-TDM utilisant le ^{18}F-FDG reflète donc l'agressivité des tumeurs. Elle est un examen de référence pour le bilan d'extension des cancers de souche folliculaire métastatiques et/ou avec histologie agressive, leur évaluation pronostique et leur suivi sous traitement. Elle peut être indiquée devant une persistance biochimique de la maladie. Sa sensibilité est cependant dépendante de la masse résiduelle mais surtout du type histologique. La TEP à l'iode 124 est en cours d'évaluation, pour sa valeur diagnostique et pour la dosimétrie. La TEP à la ^{18}F-FDOPA est à ce jour le plus sensible des traceurs pour les cancers médullaires thyroïdiens (CMT) persistants ou récidivants. Sa sensibilité est cependant dépendante de la concentration sérique de calcitonine, avec une valeur seuil autour de 150 pg/mL. La TEP au ^{18}F-FDG garde une valeur pronostique et peut être utilisée en cas de temps de doublement court de la calcitonine ou de l'ACE.
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Mots clés : Cancer thyroïdien ; TEP-FDG ; Iode-124 ; FDOPA

1. Introduction

Despite complete initial treatment, some thyroid cancer patients may have persistent disease or recurrent disease, with possible distant metastases. PET/CT is a high-resolution functional imaging technique that can guide thyroid cancer patient management. We will discuss thyroid incidentaloma detected by ^{18}F-FDG-PET, the role of ^{18}F-FDG-PET in thyroid cancers of follicular origin and the use of PET imaging for medullary thyroid carcinoma (MTC).

2. Thyroid incidentaloma on ^{18}F-fluorodeoxyglucose PET (^{18}F-FDG-PET)

It is not uncommon to identify intrathyroid ^{18}F-FDG uptake on PET examinations performed in oncology context or not, also

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http://dx.doi.org/10.1016/j.ando.2016.10.002
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called thyroid incidentaloma. Diffuse and homogeneous tracer uptake is usualy related to thyroiditis. In contrast, intrathyroid focal uptake must be further investigated since it can be due to a primary thyroid carcinoma cancer in about a 1/3 of cases, even in a context of extrathyroid oncology [1]. It warrants cytologic documentation in case of supra-centimeter lesion and if a specific treatment would be consistent with the patient prognosis.

3. PET for thyroid cancer of follicular cell origin

3.1. Stadification and restadification

During disease follow-up, the rise or persistence of abnormal thyroglobulin (Tg) level most often corresponds to lymph node metastases. It may lead to an empiric treatment with iodine-131 (^{131}I) in absence of identified resectable tumor mass. In this situation, it is not uncommon to get no abnormal ^{131}I focus on post-therapy whole body scintigraphy (^{131}I PT-WBS). ^{18}F-FDG-PET can play a role in the diagnosis of tumor persistence/recurrence. In this setting, Leboulleux et al. found 16% sensitivity for ^{131}I scan vs 88% for ^{18}F-FDG-PET [2]. This study gathered 34 patients, including 50% of stage III disease and 24% of aggressive histology sub-types. The median Tg level (in the absence of TgAb) measured after thyroid hormone withdrawal (THW) on the day of the empiric ^{131}-I administration was 47 ng/mL (range: 4–3230; mean: 290). Only one patient had a normal ^{18}F-FDG-PET and an abnormal ^{131}I PT-WBS. Therefore, the authors suggest to start with ^{18}F-FDG-PET and to proceed to empiric ^{131}I treatment only in case of negative ^{18}F-FDG-PET finding.

We will now focus on the factors influencing the pre-test probability.

In most of the studies, a non-stimulated Tg level greater than 10 μg/L is often recognized as having a sufficient pretest probability to get information on ^{18}F-FDG-PET with a therapeutic impact [3–5]. ^{18}F-FDG-PET sensitivity varies with Tg level, reflecting tumor burden in the majority of cases. Indeed, studies reported values rising from 53 up to 85% when Tg varies from 5.5 up to 29 μg/L [5–7]. A meta-analysis gathering 25 studies including 789 patients with biochemical residual disease but negative ^{131}I WBS, reported a ^{18}F-FDG-PET sensitivity and specificity of 88.5% and 84% respectively [8]. The pre-test probability increases in case of aggressive histology (mostly tall cell papillary carcinoma) [9], a locally advanced disease [10], Tg level and a short Tg level doubling time [10–12] or presence of persistent anti-Tg antibodies [13].

As ^{18}F-FDG uptake is not specific of neoplasic lesions, inflammatory nodes in the neck may be responsible of false positive results. Therefore, cytology examination and Tg measurement in (ultrasound guided) fine-needle aspiration is warranted on suspected lesions before surgical resection. When Tg is highly increased, a thoracic scan should complete ^{18}F-FDG -PET in order not to miss small pulmonary nodules that may not be seen on the CT component of PET-CT performed in spontaneous breathing, or would be responsible of false negative on PET imaging due to partial volume effect.

The role of rhTSH before ^{18}F-FDG-PET remains unclear as there has been no study reporting a significant impact of stimulation on ^{18}F-FDG-PET sensitivity. Leboulleux et al. observed more lesions per organ in the rhTSH arm but not more patients, leading to a change in disease management in only 6% of the patients [14]. Therefore, rhTSH stimulation before ^{18}F-FDG-PET should not be systematically performed. However, concomitant ^{18}F-FDG-PET can complete stimulated ^{131}I PT-WBS [10]. Indeed, in a group of 38 patients with aggressive thyroid carcinoma (45% tall cells and 42% poorly differentiated), 41% of the lesions were only seen on ^{18}F-FDG-PET and 31% on ^{131}I PT-WBS [9].

The lack of sensitivity of ^{131}I scan can be partially corrected by high resolution iodine-124 PET (^{124}I-PET). As expected, studies such as Van Nostrand's showed a superiority of ^{124}I-PET when compared to diagnostic planar ^{131}I WBS [15]. In contrast, when ^{124}I-PET is compared to ^{131}I PT-WBS, the results are highly variable [16–20]. Discrepancies are observed especially on cervical lymph nodes, but more surprisingly in case with miliary lung dissemination obviously seen on ^{131}I PT-WBS but totally missed on ^{124}I-PET [21]. So far, two studies compared ^{124}I-PET and ^{131}I PT-SPECT-CT [19,20]. In the study from de Pont et al. including 20 patients, per-patient analysis found 5% complete discordance and 45% partial discordances between both imaging modalities and ^{124}I-PET was still the most sensitive imaging modality but missed one lung miliary. On the other side, Ruhlmann et al. gathered 137 patients and found a 95% level of agreement. Khorjekar et al. [18] reported the most surprising results with 12 patients having high stimulated Tg (median: 60 ng/mL; min 0.2–max 2480) but normal "diagnostic" no abnormal focus on 74 MBq ^{131}I WBS and 63.9 MBq ^{124}I-PET. When patients underwent ^{131}I therapy, ^{131}I PT-WBS demonstrated suspicious foci in 10/12 patients. Therefore, a negative ^{124}I-PET failed to rule out the need of empiric radioiodine therapy.

The first explanation could be related to the too low amount of injected activity. ^{124}I administered activities vary from 28 up to 74 MBq, and is injected or ingested. Beijst et al. investigated on phantoms whether the reported discrepancies may be ascribed to a difference in lesion detectability between ^{124}I PET/CT and ^{131}I SPECT/CT and, hence, whether the administered ^{124}I activity is sufficient to achieve equal detectability estimated with the detectability equivalence percentage (DEP) [22]. An activity of 90 MBq is sufficient to achieve similar detectability for lesion diameters of up to 17 mm on PSF TOF PET, with DEPs up to 1.8%. On the basis of DEPs of 3.5% for lesion diameters of up to 17 mm on no-PSF no-TOF PET, ^{124}I activities as high as 170 MBq may be warranted to obtain equal detectability.

The second explanation could also be the way of stimulation before ^{124}I PET/CT. Van Nostrand et al. found in a limited number of patients that thyroid hormone withdrawal would significantly enhance the number of foci on ^{124}I-PET when compared to rhTSH stimulation [15]. The percentages of patients having positive foci detected on the 62.9 MBq rhTSH ^{124}I-PET and THW ^{124}I-PET scans were 29% (7/24) and 63% (10/16), respectively ($P < 0.03$), which was also observed with the 74 MBq ^{131}I WBS.

When ^{18}F-FDG-PET and ^{124}I-PET are performed in patients with elevated Tg level but no lesion identified on neck ultrasound, discrepancies were observed in 2/3 of the 20 included patients [23]. Sensitivities were 80% for ^{124}I-PET, 70% for ^{18}F-FDG-PET and 91% respectively for both modalities combination.

However, we do need to remind that most thyroid cancers have a good prognostic and that repeated examinations during patient follow-up has been found to be increased these last decade without any change on patients overall survival [24].

3.2. Prognostic value

In 10% of patients, metastases may occur at initial stage or during patient follow-up. An intense ^{18}F-FDG tumors uptake phenotype is associated with resistance to ^{131}I and in consequences worsens patient survival, as first demonstrated by Robbins [25,26]. Indeed, Lazar et al. demonstrated a decrease in iodine/sodium symporter expression whilst an increase in glucose transporter Glut1 in dedifferentiated thyroid tumor cells, also called on functional imaging a "Flip-flop" phenomena (Fig. 1) [27]. Poorly differentiated often demonstrate intense ^{18}F-FDG tumor uptake [28,29], up to 100% of anaplasic thyroid carcinoma [30]. ^{18}F-FDG-PET is the reference for imaging disease extension of poorly differentiated carcinoma and to metabolically characterize metastases. Once again, it completes ^{131}I WBS and therefore can be systematically performed concomitantly to ^{131}I therapy in case of bad prognosis histology.

3.3. Therapeutic monitoring

Patients with progressive refractory thyroid cancer should be treated with tyrosine kinase inhibitors (TKI) which also act as antiangiogenic agents. ^{18}F-FDG-PET scans may help in evaluating treatment response. Thus, RECIST 1.1 criteria consider as progressive disease, the occurrence of a new focus of ^{18}F-FDG uptake which has to be confirmed on CT or MRI. The next step will be the systematic use of PERCIST criteria into clinical trials [31].

3.4. Perspectives

The "Flip-Flop phenomena" can be reversible. Indeed, NIS expression inhibition related to MAP-kinase activations can be blocked by some TKI such as a MEK inhibitor [32,33]. After 1-month treatment with selumetinib, ^{124}I-PET demonstrated a significant increase in iodine uptake in 12/20 iodine refractory patients, allowing for new ^{131}I treatment in 8 patients following dosimetry studies. In one patient presenting with BRAF mutated tumors, lung metastases and one cervical node even became ^{124}I avid after treatment leading from negative to highly positive ^{124}I-PET.

Dosimetry studies rely on quantification and estimation of residence time of the radioactivity in the tumors and normal organs. Quantification is more established with PET/CT than with SPECT/CT imaging, and iodine 124 has a 4.2 days period allowing for repeated acquisitions over a few days to evaluate residence time. This makes ^{124}I-PET the best tool for dosimetry studies as described by Freudenberg [34]. There are 2 different ways of dosimetry planification and to calculate the ^{131}I activity to be administrated. The first is to define the most efficient absorbed dose in the tumors to reach tumor lysis (mostly 100 Gy for distant metastases). The second is to give the greatest ^{131}I activity limited by the threshold of toxicity defined in normal tissues (exemple: 2 Gy to the bone marrow). Sgouros et al. have recently integrated radiobiological data about radiosensitivity of different tissues obtained from external beam radiation [35].

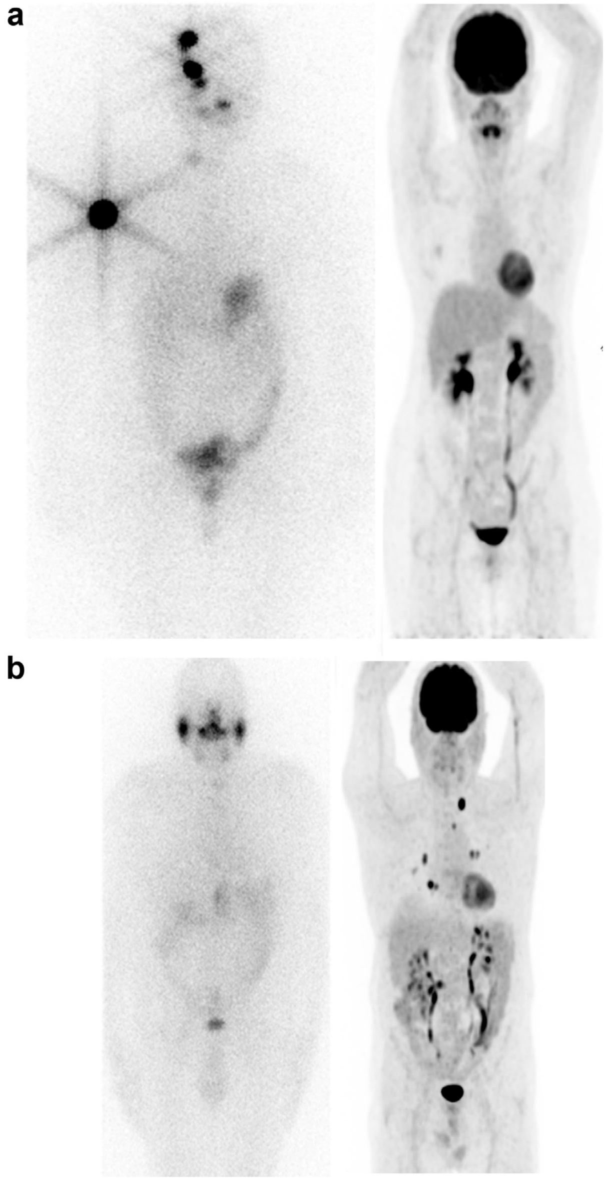

Fig. 1. "Flip-flop phenomen": complementarity of ^{18}F-FD-PET and post-therapeutic Iodine 131 scan. a. Patient presenting with bone metastases in the right temporal bone and right humeral head demonstrating intense Iodine 131 uptake (1.a.1) but no ^{18}F-FDG uptake (1.a.2). b. Patient presenting with lymph-nodes and lung metastases demonstrating no Iodine 131 uptake (1.b.1) but an intense ^{18}F-FDG uptake (1.b.2).

4. Medullary thyroid carcinoma (MTC)

MTC often metastases in cervical nodes leading to iterative surgical resections. Unfortunately, persistent disease is observed in many cases despite these approaches. The patient is then monitored with repeated multimodal imaging including cervical-thoracic calcitonin (CT), liver and bone marrow MRI, due to the risk of diffuse multiple organ extension [36]. The rhythm for surveillance depends on markers (CT and/or CEA) doubling time. A less than 1 year doubling time is associated with worse prognosis. Only in that situation, ^{18}F-FDG-PET can reveal significant tracer uptake in metastases, stressing again the prognostic value of ^{18}F-FDG-PET [37].

^{18}F-FDOPA-PET was expected to help in the diagnosis of metastatic sites. However, its sensitivity varies from 47% up to 83% as reported by Treglia [38], depending on CT levels. As reported in the review by Slavikova, ^{18}F-FDOPA accuracy becomes significant if CT is greater than 150 pg/mL [39]. In the study of Archier et al., none of the 10 patients having only abnormalities on ^{18}F-FDOPA in nodal necks normalized CT level after surgery [40]. The lymph node compartment-based sensitivity of ^{18}F-DOPA PET/CT was 100% but lesion-based sensitivity was only 24%. Early acquisitions are mandatory as a tumors washout is often observed [41]. ^{18}F-FDOPA PET might also reveal a synchronous pheochromocytoma in MEN2 patients. Somatostatin analogues radiolabeled with Gallium 68 have been even less successful [42,43]. However, it may select patients for peptide radionuclide therapy (PRRT) in case of significant lesions uptake. Treglia has compared the 3 different radiotracers, and ^{18}F-FDOPA remains the most sensitive tool [38,42].

Calcitonin remains a highly sensitive biomarker, highly more sensitive than any radiological examination. Therefore, stable high level of CT without detectable lesions would not alter patient short-term outcome, and should lead to a loose surveillance. Furthermore, apart from general symptoms such as profuse uncontrolled diarrhea, TKI are only indicated in case of supra-centimetric lesions visible on conventional imaging, and having a significant progression on RECIST over the last 12 months. At present, this still limits the value of functional imaging for the management of MTC.

Table 1
Use of PET for thyroid cancers.

Follicular thyroid carcinoma
  ^{18}F-FDG-PET
    Initial staging of poorly and undifferenciated carcinoma
    Recurence diagnostic
      In case of agressive tumor (mostly tall cells)
      And/or in case of non-stimulated Tg > 10 ng/mL
      And/or in case of greatly increased Tg antibodies level
    Prognostic evaluation of metastatic disease.
    Iodine refractory disease follow-up
  PET with iodine 124: under investigation for dosimetry purpose
Medullary thyroid cancer
  ^{18}F-FDOPA PET for metastases diagnostic when CT > 150 pg/mL
  ^{18}F-FDG-PET for metastatic disease prognosis in case of CT or CEA doubling time < 1 year

5. Conclusion

In conclusion, PET imaging complements morphological imaging in the management of thyroid cancer of follicular origin, mainly for aggressive histologic subtypes (Table 1). Its role for medullary thyroid carcinoma is still debated and not well positioned.

Disclosure of interest

The authors have not supplied their declaration of competing interest.

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Annales d'Endocrinologie 78 (2017) 43–53

Annales
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Consensus

Consensus statement on the management of dyslipidaemias in adults[☆]

Working group commissioned by the the French Society of Endocrinology (SFE) Francophone Society of Diabetes (SFD), The New French Society of Atherosclerosis (NSFA), S. Béliard[a], F. Bonnet[b], B. Bouhanick[c], E. Bruckert[d], B. Cariou[e], S. Charrière[f], V. Durlach[g], P. Moulin[f,*], R. Valéro[a], B. Vergès[g,h]

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Keywords: Dyslipidemia; Cardiovascular risk; Statins; Fibrates; Consensus statement; LDLc goal

1. Introduction

Most cases of dyslipidaemia increase the risk of ischaemic cardiovascular (CV) complications, while their treatment can reduce CV morbidity and mortality. There is, therefore, a broad international consensus for promoting treatment, although with some variations in approach. As previous French recommendations for dyslipidaemia treatment date back 10 years, they are no longer up to date and have been retracted. However, the complex and evolving differences between the recommendations of European societies (EAS/ESC) [1–3], the International Atherosclerosis Society (IAS) [4], and national bodies in the US (AHA/ACC) [5,6] and Great Britain (NICE) [7] mean that it has become necessary for practitioners to have an updated consensus statement informed by the latest clinical trials.

Thus, a synthesis integrating features from both American and European recommendations was created. A condensed version for the sake of simplicity is presented here, although readers may refer to the primary source documents via the references selected by members of the working group (WG). This consensus statement concerns the general population and does not address either familial hypercholesterolaemia [8–10] or diabetic dyslipidaemia [11,12] in detail. This text is consistent with the opinions of the WG, and has been validated by external readers from three of the societies involved and based on data from the literature available up to 2016.[1]

2. Initial evaluation

2.1. *Identification of secondary dyslipidaemia*

Secondary dyslipidaemia must be ruled out through investigation of the diseases and treatments that could cause hyperlipidaemia. This involves checking, when appropriate, thyroid-stimulating hormone (TSH), blood glucose, urine protein by dipstick and creatininaemia. Hypothyroidism and cholestasis can induce hypercholesterolaemia; however, the clinical context of cholestasis is generally suggestive. Nephrotic syndromes can cause severe mixed hyperlipidaemia. Diabetes, renal insufficiency and excessive alcohol consumption result

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[☆] A French version of this consensus was published in the *Revue du praticien* (September issue).

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[1] Grading the recommendations was done using the HAS scoring system from A to C for decreasing levels of strength, and from 1 to 3 for quality evaluation of the literature on which it is based.

http://dx.doi.org/10.1016/j.ando.2016.11.001
0003-4266/© 2016 Published by Elsevier Masson SAS.

Table 1
Major cardiovascular risk factors (CVRF) to be considered in subjects with dyslipidaemia.

CVRF
Age (men $\geq$ 50 years, women $\geq$ 60 years)
Ischaemic CV family history (men $\leq$ 55 years, women $\leq$ 60 years)
Current smoker or quit for < 3 years
Hypertension
HDLc $\leq$ 0.40 g/L ($\leq$ 1.0 mmol/L)
Type 2 diabetes (or type 1 diabetes for > 15 years and age > 40 years)
Renal failure (GFR < 45 mL/min, < 60 mL/min in young adults)

HDLc: high-density lipoprotein cholesterol; GFR: glomerular filtration rate.

in hypertriglyceridaemia. The main treatments that increase low-density lipoprotein cholesterol (LDLc) and, often, triglycerides (TG) are cyclosporin, retinoids, corticosteroids, oral ethinylestradiol, certain antiretrovirals, certain neuroleptics and certain targeted therapies in oncology.

2.2. *Estimation of CV risk*

CV risk needs to be taken into consideration for adjusting the intensity of primary prevention measures (before the occurrence of atherothrombotic complications). Indeed, the risk/benefit ratio of the treatment and its efficacy (number of persons to be treated to avoid ischaemic complications) depend on the magnitude of the expected benefit. This is based on the level of absolute risk of the individual concerned. Risk-calculation models refer to the multifactorial risk of the general population and not to monogenic primary dyslipidaemias, such as familial hypercholesterolaemia, for which the level of risk is underestimated with general models. Risk-calculation models specific to diabetes patients are also available [13–15].

In practice terms, the WG recommends risk evaluation of the general population based on SCORE tables, which estimate the risk of ischaemic CV death at 10 years [adjusted for low-risk European countries, including France, and taking into account high-density lipoprotein cholesterol (HDLc)] [16]. When such tables are not available, the WG suggests pragmatic tallying of the standard cardiovascular risk factors (CVRF) as a substitution method (low CV risk: 0–1 CVRF; intermediate risk: 2 CVRF; high CV risk: $\geq$ 3 CVRF).

2.2.1. *Risk factors and markers*

The main CVRF to be taken into consideration in patients with dyslipidaemia are age and gender, family history of CV disease (first-degree relatives), tobacco use, arterial hypertension, decreases in HDLc, the presence of diabetes and severe to moderate chronic renal failure (CRF), (Table 1). These all contribute to risk estimation and treatment decision-making.

2.2.1.1. Lipid tests. Lipid tests are needed at the baseline assessment for estimating the individual level of risk, and then during follow-up to evaluate the efficacy of treatment to ensure adherence, to motivate patients with respect to dietary and lifestyle measures, and to guide potential treatment intensification (A1) (Table 1)[2]. It is possible to conduct non-fasting lipid tests when the practitioner finds it necessary to facilitate screening in an elderly person or after an acute coronary syndrome (ACS) [17]. Reliability of the LDLc estimate is all the more affected when there is postprandial hypertriglyceridaemia. Although the role of HDLc as a contributory factor of CV protection has been called into question, its plasma determination provides a powerful marker of CV risk and must therefore be maintained in CV risk assessment (A1) [18].

Table 2
Indications for lipoprotein(a) [Lp(a)] assay.

Intermediate or high ischaemic cardiovascular (CV) risk with
Early personal CV history
Recurrent ischaemic CV complications despite effective treatment with statins
Familial hypercholesterolaemia (heterozygous familial hypercholesterolaemia)
Family history of increased Lp(a)

Adapted from Catapano et al. [1], Stone et al. [5] and Nordestgaard [20].

Although no large-scale, double-blind clinical trials have been done with titration of a lipid-lowering treatment to attain an LDLc target, reference markers are necessary for determining the at-risk subject's condition at inclusion and with treatment in relation to levels observed in CV prevention trials (C3). Cholesterol measurements unrelated to HDL [total cholesterol (TC) – HDLc] may be used in the event of hypertriglyceridaemia (HTG). This takes remnants into account and does not require LDLc assay; its value is 0.3 g/L (0.77 mmol/L) above the usual reference values used for LDLc (B2) [19]. Assay of apolipoprotein B (ApoB) plasma concentration does not provide major advantages for estimates of CV risk (B2). Its main clinical relevance is limited to the aetiological diagnosis of mixed hyperlipidaemia to differentiate familial combined hyperlipidaemia from dysbetalipoproteinaemia, in which ApoB is not increased.

Measurement of lipoprotein (a) [Lp(a)], a risk cofactor for familial hypercholesterolaemia and unexplained atherothrombotic states, should not be done systematically, as its assay indications are restricted (Table 2) [20].

2.2.1.2. Limitations and benefits of other risk markers. The benefits of employing other risk marker assays for clarifying the risk of subjects with dyslipidaemia remain a matter of debate.

2.2.1.2.1. Biological markers. Plasma concentration assays of fibrinogen, ultrasensitive C-reactive protein (us-CRP) [21], homocysteine (excluding unexplained atherothrombotic complications), lipoprotein-associated phospholipase A2 (Lp-PLA2) [22], lipoparticles (such as LpA1), and the identification of small dense LDL and microalbuminuria (apart from diabetes or hypertension) provide no adequate additional predictive value in dyslipidaemic patients.

2.2.1.2.2. Genotyping. In primary (genetic) hyperlipidaemia, genotyping patients at specialized expert centres enables characterization of the relevant disease (investigation of genetic variants of, for example, LDLR, APOB, PCSK9, APOE and LPL) and may soon be used to determine access to specific treatments. However, available studies of the many genetic polymorphisms associated with high CV risk do not substantially improve prediction of CV risk. Consideration of family history has a more relevant integrative effect at this time [23,24].

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[2] Quotes (A1, B3) correspond to the level of evidence based medicine regarding the recommendation and quality of the literature.

2.2.1.3. Functional exploratory studies. In cases of intermediate risk, consideration of additional risk markers indicating premature subclinical atheroma can be used to reclassify subjects into high- or low-risk categories.

2.2.1.3.1. Stress tests. Stress tests do not play a role in estimating CV risk in the asymptomatic general population. Its indications pertain to monitoring of high- or very high risk patients with either symptomatology suggestive of coronary insufficiency, suspicious electrical abnormalities on baseline ECG or a particularly high probability of silent myocardial ischaemia, as seen in certain subgroups of diabetics. Performance of a stress test is also indicated in the resumption of vigorous physical activity in sedentary subjects with high CV risk.

2.2.1.3.2. Myocardial scintigraphy, stress echo test, dobutamine stress echo tests. These exploratory studies, besides the irradiation and costliness of scintigraphy, are not first-line tests designed to stratify CV risk through the identification of subclinical coronary insufficiency in asymptomatic dyslipidaemic patients [25].

2.2.1.3.3. Exploratory studies of vascular function. Carotid–femoral pulse wave velocity, in which acceleration indicates arterial rigidity, provides insufficient additional value in terms of reclassifying CV risk in normotensive dyslipidaemic subjects, although it may be considered relevant in those with hypertension (B2) [26]. Determination of arterial vasodilatation is part of clinical research due to its difficulty and variability. Systematic measurement of the systolic pressure index (SPI) in subjects with low-to-intermediate risk provides an insufficient level of CV risk reclassification [27,28]. SPI measurement is a supplementary examination done during Doppler ultrasound for arteriosclerosis obliterans (AO), but is not advisable in dyslipidaemic subjects without a clinical suspicion of AO (B3).

2.2.1.4. Imaging.

2.2.1.4.1. Carotid ultrasound. Measurement of carotid intima media thickness (IMTc), which is invaluable in clinical research as an integrated marker of risk, has insufficient predictive value in clinical practice for adjusting the prediction of CV events. Moreover, variability of its measurement due to the method of acquisition and software used hampers comparisons of two separate measurements [21,29]. The ability to reclassify ischaemic risk is limited, and its use in clinical practice is not recommended (B2). Detection of significant carotid plaques, however, may be a predictive integration tool and an opportunity to screen for severe carotid stenosis [30,31]. Nevertheless, severe stenosis is rare and usually arises in the context of high CV risk and/or confirmed polyvascular atheromatous disease. The WG recommends carotid ultrasound with plaque assessment when there is no access to a multislice computed tomography (CT) scan equipped to measure coronary calcium scoring in intermediate-risk patients (B2).

2.2.1.4.2. Coronary calcium scoring. Quantification of coronary calcifications using a CT scan without contrast injection is a method that uses little irradiation. A very high load of calcified atheromatous plaques suggests the presence of multiple non-calcified plaques (stenotic or non-stenotic); such a finding translates into a level of risk that may be equivalent to that observed in secondary prevention (A1). The results must be interpreted both as an absolute value (very high individual risk when the score exceeds 300–400 AU) and a relative value compared with the score of a similar population to assess the additional relative risk (calcium score > 75% for age and gender) [32]. A zero score has a strong negative predictive value for CV ischaemic events. The level of reclassification is high in subjects with intermediate risk [23]. Its use could be effective for optimizing CV preventative measures in conditions of intermediate risk [33]. The WG recommends its use in this particular situation (B2).

2.2.1.4.3. CT coronary angiography. CT coronary angiography is not indicated in asymptomatic dyslipidaemic patients for assessing subclinical coronary atheroma except for unusual circumstances (C2). However, it may be used in subjects suspected to have stable coronary disease and who are at intermediate risk (B1). A functional test for investigating myocardial ischaemia is generally preferred (A1) [34].

3. Dietary approaches

Dietary measures are to be systematically implemented overall for both secondary and primary prevention once LDLc is > 1.3 g/L (3.34 mmol/L, median for French adults) or when serum TG levels are > 1.5 g/L (1.7 mmol/L, 90th percentile) (A1).

Individualized lifestyle modifications combining physical activity and supervised dietary intakes aimed at nutritional balance and not systematic weight loss [35] could have an impact on long-term CV risk [36,37]. Recommendations consist of implementing a Mediterranean-type diet, including olive oil and nuts (walnuts, hazelnuts, almonds, 30 g/day), which currently has the highest level of proof (A1) [38].

3.1. General nutritional recommendations for CV prevention

3.1.1. Lipid intakes

Total recommended lipid intake is around 25–35% of total caloric intake in adults (A2):

- saturated fatty acids (SFA) increase LDLc, and daily intakes should not exceed 8–10% of energy requirements [39,40]; they should be replaced with oleic acid and polyunsaturated fatty acids (A1) [41];
- trans-unsaturated fatty acids promote an increase of LDLc and decrease of HDLc. Their intake should be as low as possible from processed sources (< 1%) [42];
- mono-unsaturated fatty acids decrease LDLc as a substitute for SFA. Several studies related to the Mediterranean diet suggest beneficial effects with olive oil consumption for

preventing CV events, and an intake of about 15% of total energy intake (TEI) is recommended (A1) [43];

- polyunsaturated fatty acids lower LDLc and, to a lesser extent, HDLc when they replace SFAs. When used excessively in the form of vegetable oil [omega-6 fatty acids (FA)], they upset the omega-3/omega-6 FA balance. An increased ratio is recommended at the expense of SFAs, but they should not exceed 10% of TEI (A2) [44];

  Note: There is a very limited level of proof for supplementing with alpha-linolenic acid (ALA) and/or long-chain omega-3 FA (EPA, DHA) above the reference nutrient intake (RNI), according to several recent randomized trials [45]. The WG does not recommend the use of dietary supplements provided that nutritional needs (RNI) are met by a diversified diet, including fish (B1).
- reducing high-cholesterol foods has a variable effect on LDLc that is less than those obtained by adjusting the composition of FA. Moderation to < 300 mg/day is a common-sense measure recommended particularly with mixed intakes rich in SFAs, cholesterol and sodium chloride (such as cold cuts) (B2) [39].

3.1.2. Fibre intake

A daily intake of 30–45 g of fibre, including 5–15 g/day of soluble fibre, is recommended. Preference should be given to daily consumption of fruit (two portions) and vegetables (three portions) (A2) [46,47]. High intakes of fruit/fruit juices may increase hypertriglyceridaemia.

3.1.3. Alcohol consumption

As long as alcohol consumption is low to moderate [0.5–2 U/day (1 U = 10 g pure alcohol)], it is not discouraged as a CV preventative strategy due to its established association with a moderate reduction of CV risk [48]. This relationship, however, does not demonstrate causation and is independent of the type of alcohol ingested; meta-analyses of observational studies do not show a significant decrease in CV mortality [49].

3.2. Dietary supplements

3.2.1. Phytosterols

Supplementing with phytosterols remains controversial due to the lack of interventional studies for CV events [50]. At an effective dose (2 g/day), they lower LDLc by 10% [51]. There is no consensus within the WG on their systematic use in patients with hypercholesterolaemia or a high CV risk (C3) [52,53].

3.2.2. Red yeast rice (RYR)

RYR is in fact lovastatin, a first-generation statin, at low doses. The cholesterol lowering effect is not as strong as with statins with marketing authorization (MA), and the production process has not been perfected. Its safety profile is poorly documented. At present, the WG refers to warnings by the ANSM (National Agency for the Safety of Medicines and Health Products) and ANSES (French Agency for Food, Environmental and Occupational Heath and Safety), and does not recommend the use of RYR products in the absence of sufficient quality-control procedures [54,55].

3.2.3. Policosanol

This has no conclusive cholesterol lowering effect, according to the latest, strictly controlled studies. Its use is therefore not recommended [56].

3.3. Influence of lifestyle on TG levels

It is recommended that there be a focus on weight reduction through physical activity and a balanced low-calorie diet in cases of overweight or obesity. The effects of discontinuing alcohol consumption are yet to be evaluated [57].

The proportion of carbohydrates in relation to TEI is limited to < 50%. Intakes of mono- or disaccharide simple sugars, particularly fructose, is reduced to < 10% of TEI. In cases of hypertriglyceridaemia, the consumption of sugary drinks is not recommended (sodas, fruit juice), and fruit should be taken in moderation (one per meal). When additional TG-lowering effects are desired through supplementing with omega-3 long-chain FA, only high intakes that are considerably greater than the RNI (≥ 2 g/day) have shown any such effects (B2).

Major hypertriglyceridaemia includes the risk of acute pancreatitis, which is considered moderate with TG levels > 10 g/L (11.3 mmol/L) and high with levels > 30 g/L (34 mmol/L). The implementation of strict fasting until TG levels return to the safe range is therefore a nutritional emergency (A3). It is advisable to seek a specialized opinion for possible additional exploratory tests and to choose a subsequently relevant dietary approach: for example, a diet drastically low in fat vs. a balanced low-calorie diet low in simple carbohydrates.

4. Primary prevention of hypercholesterolaemia and mixed dyslipidaemia

Risk-calculation tables are inadequate in heterozygous familial hypercholesterolaemia in both children and adults, as they do not incorporate duration of exposure to hypercholesterolaemia and, thus, underestimate the risk, particularly in young adults. There are specific recommendations for the diagnosis and therapeutic indications [8–10]. Screening for dyslipidaemia in first-degree relatives is recommended when LDLc is > 1.9 g/L (4.9 mmol/L) in an index case that establishes the diagnosis of familial hypercholesterolaemia. Clinical and biological predictive scores may support the aetiological diagnosis. It is essential to refer cases of severe heterozygous familial hypercholesterolaemia and children to specialized centres.

4.1. General treatment recommendations

Dietary measures are recommended for all patients except those with LDLc < 1.3 g/L and low CV risk (SCORE < 1%) (A1). In addition to dietary measures and promotion of regular physical activity, smoking cessation support is an important component of the CV prevention process (A1) [2].

For primary prevention in the general population, treatment decisions depend on 10-year CV risk assessment (SCORE calculation or tables, cumulative CVRF) (A2).

Table 3
Situations with increased risks of muscle-related side-effects (non-exclusive list of indications).

Renal or hepatic failure
History of previous muscle intolerance to lipid-lowering agent
History of myopathy
Preexisting increase of creatine phosphokinase > 3 times normal
Treatment with drugs that interfere with statin metabolism (immunosuppressors, antiretrovirals)
Hypothyroidism
Age > 75 years
Asian origin
Chronic alcohol use

Adapted from Catapano et al. [1], Stone et al. [5] and Hegele et al. [57].

Table 4
Treatment with statins according to their intensity.

Low-intensity statin treatment	Moderate-intensity statin treatment	High-intensity statin treatment
LDLc decrease < 30%	LDLc decrease < 50%	LDLc decrease > 50%
Fluvastatin 20–40 mg Pravastatin 10–20 mg Simvastatin 10 mg	Atorvastatin 10–20 mg Fluvastatin 80 mg Pravastatin 40 mg Simvastatin 20–40 mg Rosuvastatin 5–10 mg	Atorvastatin 40–80 mg Rosuvastatin 20 mg

Adapted from Stone et al. [5].
LDLc: low-density lipoprotein cholesterol.

The first-line drug treatment is a statin (A1). For primary prevention, a gradual increase in statin doses is recommended until the target is reached. In cases of intolerance, as confirmed by testing other statins at low doses, or a contraindication to statins, treatment alternatives are ezetimibe or even cholestyramine (B3) [58].

Treatment efficacy and compliance are monitored through lipid testing at 1–3 months and then annually once LDLc is on target and clinical tolerability is satisfactory. During the initial treatment phase, transaminases and blood glucose are measured; creatine phosphokinase (CPK) is checked only in the event of clinical signs or in subjects at risk of muscle complications (Table 3).

4.2. LDLc objectives and CV risk in primary prevention

The LDLc concentrations presented in Fig. 1 are thresholds for intervention or intensification, as well as the minimum target to be achieved.

4.2.1. Low CV risk [according to SCORE calculation: risk of CV death at 10 years < 1% or 0–1 CVRF (excluding diabetes)]

Statin treatment is overall rarely justified with low CV risk due to lack of effectiveness. The intervention threshold is 1.9 g/L (4.9 mmol/L), and treatment with a low-intensity statin (Table 4) is generally sufficient (A1).

4.2.2. Intermediate CV risk (risk of CV death at 10 years between ≥ 1 and < 5% or 2 CVRF)

The threshold is 1.30 g/L (3.4 mmol/L) (B2). This also includes diabetics with no additional risk factors. Statin treatment is usually advisable in this situation.

The HOPE-3 clinical trial explored primary prevention with intermediate risk (CV mortality in the placebo group projected over 10 years: 5.1%) and showed the effects of rosuvastatin 10 mg/day on major ischaemic CV events. Mean LDLc at inclusion was 1.27 g/L, with a mean LDLc decrease of 0.35 g/L vs. placebo [59,60].

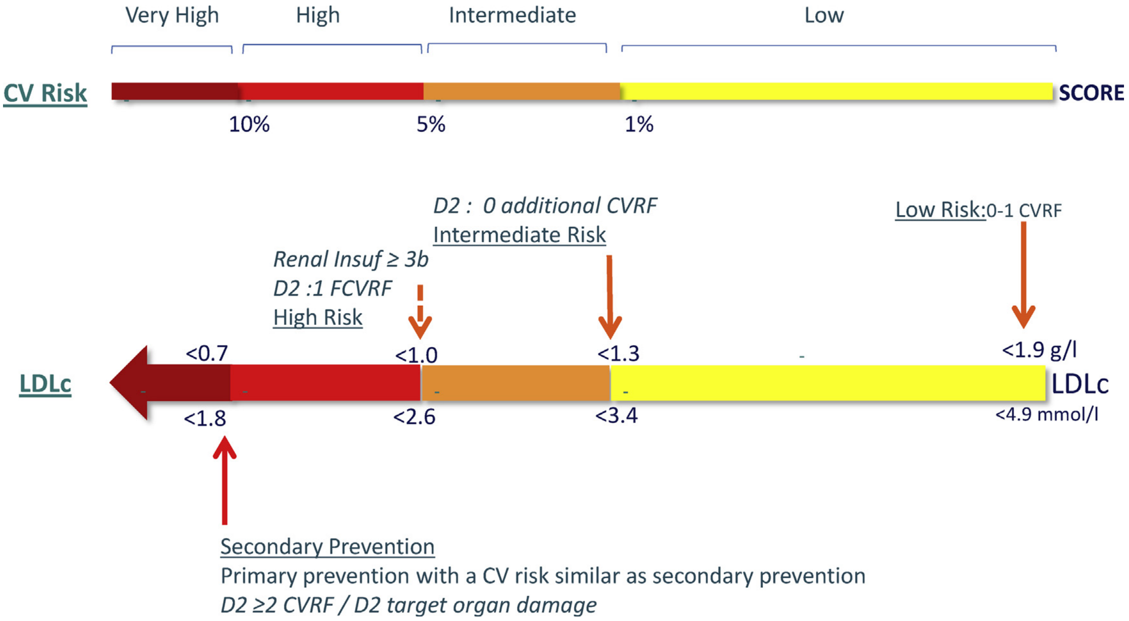

Fig. 1. Treatment options in the presence of hypercholesterolaemia. CV: cardiovascular; CVRF: cardiovascular risk factors; D2: type 2 diabetes; LDLc: low-density lipoprotein cholesterol.

This target, however, may be adjusted, and the final decision must take into account the:

- patient's preferences;
- presence of disease associated with increased CV risk, such as chronic inflammatory disease (rheumatoid arthritis), radiation therapy including the heart area, moderate CRF [glomerular filtration rate (GFR) < 60 mL/min] in young subjects;
- presence of subclinical atheroma more serious than expected for age (verified by advanced carotid plaques or a high calcium score), as this reclassifies the subject into the high CV risk category.

4.2.3. *High CV risk (risk of CV death at 10 years ≥ 5% or ≥ 3 CVRF)*

The purpose of primary prevention treatment in these patients is to maintain LDLc at < 1 g/L (A1). This is the most commonly recommended target for type 2 diabetes, as these patients generally have at least one coexisting CVRF.

Special categories of patients at very high CV risk may warrant more ambitious targets (LDLc < 0.7 g/L). This small, select group includes patients presenting with diabetes and target-organ involvement (confirmed nephropathy, stage 2+ retinopathy: moderate preproliferative) or with > 2 CVRF in addition to diabetes (A2). In cases of haemodialysis or renal transplantation, there are no longer any indications for introducing a statin at this stage (B2); however, statins that were started previously during the severe CRF stage need not be discontinued (C2).

4.3. *Special cases of mixed dyslipidaemia*

The most recent epidemiological data suggest that hypertriglyceridaemia has independent proatherogenic effects even in the absence of diabetes or the metabolic syndrome (MetS) [61–63]. However, the atherogenicity of hypertriglyceridaemia is less intense overall than that of hypercholesterolaemia, and LDLc remains the priority target in terms of CV prevention (Fig. 2). As a result, the presence of mixed hyperlipidaemia with moderate hypertriglyceridaemia (< 5 g/L) does not change the therapeutic management for isolated hypercholesterolaemia [64,65]. The dietary and lifestyle guidelines concerning hypertriglyceridaemia are given together with those of hypercholesterolaemia, as they play particularly important roles in controlling hypertriglyceridaemia (A1). The process of using cholesterol lowering agents is the same for high or very high risk in primary prevention (B3).

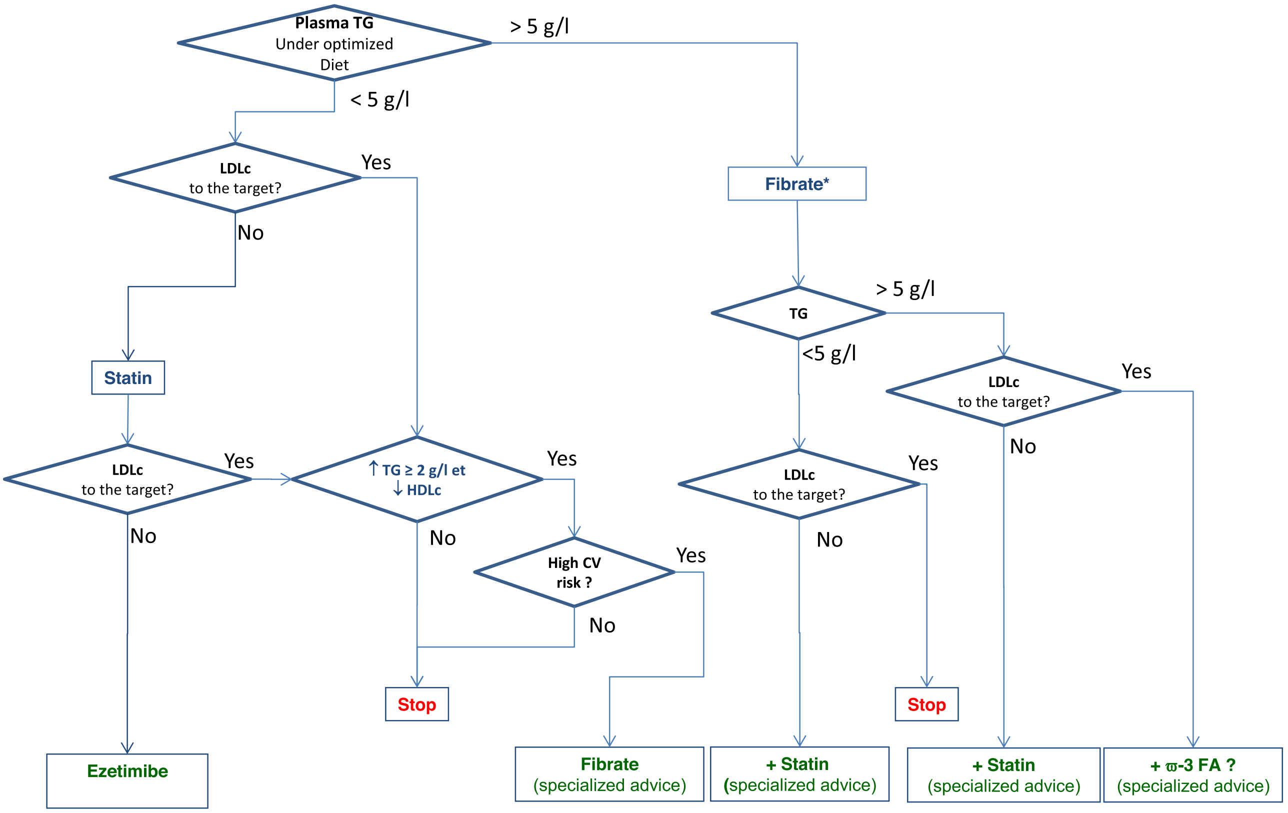

Fig. 2. Treatment options in the presence of hypertriglyceridaemia. LDLc calculation cannot be used in cases of hypertriglyceridaemia > 4 g/L. If necessary, direct measurement, ApoB assay or calculation of non-HDL cholesterol can be applied. *Only fenofibrate + statin was used in large-scale clinical trials; the combination of gemfibrozil + statin is contraindicated. CV: cardiovascular; TG: plasma triglycerides; LDLc/HDLc: low-density/high-density lipoprotein cholesterol; ω-3 FA: omega-3 fatty acids.

4.3.1. Mixed dyslipidaemia including moderate hypertriglyceridaemia [< 5 g/L (5.6 mmol/L)]

4.3.1.1. LDLc is on target using dietary/lifestyle measures and/or statins. With moderate hypertriglyceridaemia (2–5 g/L), fibrates are an option only if two other conditions are also met (B3) [66–69]: low HDLc (≤ 0.4 g/L); and high or very high CV risk.

Specialist advice is recommended for a statin/fibrate combination (B2) [70]. Due to its risk of drug interactions, gemfibrozil is contraindicated in combination with statins and, therefore, fenofibrate should be used (B3).

4.3.1.2. LDLc is not on target despite dietary/lifestyle measures and/or statins. The priority is to reach the LDLc target by using and titrating a statin (A1). If the statin is at the optimal dose and dietary/lifestyle measures have been used, yet LDLc is still not on target, then ezetimibe should be added to the statin (B2) [71].

4.3.2. Mixed dyslipidaemia including high hypertriglyceridaemia (> 5 g/L)

Use of a first-line fibrate is mainly for hypertriglyceridaemia ≥ 5 g/L and resistant to dietary/lifestyle measures, with the aim of reducing the risk of acute pancreatitis via a decrease in TG levels (B3). However, there are no controlled clinical trials to validate this hypothesis [72]. Specialist advice is necessary in cases of treatment-resistant hypertriglyceridaemia or severe hypercholesterolaemia.

5. Management of hypercholesterolaemia and mixed dyslipidaemia for secondary prevention of ischaemic CV complications

Only one randomized, open-label, study has been done using dosage titration for achieving an LDLc target < 0.8 g/L [73]. During this trial of patients with stable coronary insufficiency, mean LDLc decreased to 0.95 g/L in the intervention group vs. 1.10 g/L. Benefit was seen for the composite primary endpoint and non-fatal infarction.

Baseline plasma concentrations of LDLc and those obtained with treatment during clinical trials also provide objective reference points for directing treatments. In meta-regression interventional studies, a linear relationship is retained between the magnitude of LDLc decrease and reduction of relative risk (RR) of major ischaemic events, and the gain in RR persists in subgroup analyses of LDLc levels close to 0.7 g/L, but with a simultaneous increase in the number of people to be treated [74].

It is recommended that a high-intensity statin be used from the outset for secondary prevention (atorvastatin 80 mg), except in cases of LDLc that is not high at baseline and/or with a significant risk of muscle side effects (Table 3). The increased risk of type 2 diabetes is largely offset by the reduced risk of recurrent ischaemic complications.

An LDLc target < 0.70 g/L (1.8 mmol/L) is recommended (A2). This threshold is based on:

- results of randomized controlled trials (RCTs) testing treatment strategies using high-intensity vs. lower-intensity statin treatments [75–79];
- results of IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) [80];
- consideration of extrapolations from meta-analyses and analyses of extreme subgroups [74,81–83].

If the LDLc target is not reached by monotherapy using the maximum tolerated statin dose, the addition of ezetimibe should be considered (A2). During IMPROVE-IT, intensification of the cholesterol lowering treatment decreased LDLc from 0.7 g/L to 0.54 g/L, with a significant 2% reduction in absolute value of the primary endpoint. This enabled one major ischaemic event to be avoided through the annual treatment of 300 people [80]. Other studies are now being conducted to explore lower LDLc targets, with some proposing a target of 0.5 g/L (1.3 mmol/L). The effectiveness (cost/efficacy ratio) of such objectives needs to be evaluated.

When the maximum treatment dose fails to decrease LDLc to < 0.7 g/L, a 50% reduction of LDLc is considered an acceptable compromise [1,5]. Nevertheless, a patient who maintains a high LDLc despite such a reduction continues to have a high residual CV risk.

In the event of adverse reactions with a high-dose statin or statin–ezetimibe combination, the use of a low- to moderate-dose statin with an LDLc target < 1 g/L is recommended (C1). In the event of statin intolerance, monotherapy with ezetimibe or even cholestyramine should be used (C2).

In cases of associated hypertriglyceridaemia, the strategy considered for mixed dyslipidaemia (see Section 4.3.1 above) should be used.

If LDLc remains > 2 g/L in secondary prevention with the maximum tolerated treatment, the patient should be referred to a specialized centre for consideration of LDL apheresis (A3).

6. Other special situations

6.1. Management of isolated hypertriglyceridaemia

People with a history of major hypertriglyceridaemia (> 10 g/L) require a specialist's opinion (Fig. 2). Dietary and physical activity measures play a central role in controlling isolated hypertriglyceridaemia (A1). Secondary factors, such as diabetes and MetS, are particularly common with hypertriglyceridaemia and need to be addressed.

6.1.1. Persistent hypertriglyceridaemia ≥ 5 g/L despite dietary/lifestyle measures

A fibrate should be used as the first-line monotherapy (A1). In cases of persistent hypertriglyceridaemia ≥ 5 g/L despite dietary/lifestyle measures and fibrate therapy at optimal doses, high-dose omega-3 long-chain FA (> 2 g/day of EPA/DHA) may be added after specialist consultation (C3). While these products are no longer reimbursed in France as medications, they are available as dietary supplements. If hypertriglyceridaemia persists at ≥ 5 g/L despite dietary/lifestyle measures and fibrate therapy at optimal doses, and LDLc levels are not on target despite the patient's RR (measured by a direct method or by non-HDLc determination), a statin could be added to fenofibrate following specialist consultation (C3).

6.1.2. Moderate isolated hypertriglyceridaemia (2–5 g/L) despite dietary/lifestyle measures

CV risk estimates take precedence:

- if the risk is low to intermediate, there is no need to add a fibrate;
- if it is high with LDLc on target, the use of a fibrate should be considered, as per the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) and Helsinki Heart Study (HHS) [84,85].

6.2. HDLc $\leq$ 0.30 g/L with no secondary factors

It is important to seek a specialist's opinion for establishing the aetiological diagnosis and evaluating the opportunity for treatment. The decision is based on investigation of subclinical atheroma. If there is reclassification to a high CV risk, a statin should be proposed, although the level of proof is limited due to the lack of specific clinical trials of this setting (B3).

6.3. Elderly people (> 75 years)

When epidemiological studies are carried out with adjustment of health status indicators (albumin, iron, etc.), a positive relationship between LDLc and CV risk is found even in elderly populations [86–89]. Meta-analyses and the PROSPER study have shown CV benefit from statins in the elderly [90–92], and several cohort studies have found no increased risk of cancer or cognitive impairment.

Identification of hypercholesterolaemia in elderly subjects with no CV history should prompt investigations for possible secondary dyslipidaemia (C3).

In the elderly, initiation or continuation of treatment with a statin needs to be considered on the basis of comorbidities and the potential benefit that the treatment may provide (C2).

It is advisable to continue statin treatment after the age of 75 years in subjects who are already being treated and tolerate the treatment (B1) [5].

For primary prevention, if associated CV risk factors and advanced non-complicated atheroma are present, the use of low-dose statin treatment in those aged 75–80 years should be carefully weighed. The decision should take into account the absence of severe comorbidities; secondary hyperlipidaemia should also be ruled out and a low dose selected (B2) [1,5].

For secondary prevention, it is advisable to treat elderly subjects with a statin for an LDLc target value < 1.0 g/L (B2).

7. Conclusion

This consensus statement is based on information that has heterogeneous levels of proof and is supported by analyses of the continually evolving literature. Genetic dyslipidaemia has specific recommendations, as estimates of risk and treatment implications differ. There are specific consensuses for these situations. The present synthesized recommendation addresses the general population of subjects with dyslipidaemia and CV risk. Given the prevalence of diabetes and renal failure and their attendant CV risks, and the secondary dyslipidaemia observed in these situations, some reference markers have been provided for these populations, including specific recommendations for their management. Following the emergence of generic statins, and the subsequent period of cost reductions, for the treatment of dyslipidaemia, the development of new, more expensive, drugs will soon require reevaluation of certain indications with the aim of providing optimal management and treatment based on efficacy as well as cost.

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Disclosure of interest

The participants declare having scientific activities involving earnings or research funding (conferences, clinical trials or research grants) during the years 2012–2016.

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Acknowledgements

The logistics related to setting up these guidelines were supported by an unrestricted grant from the French Society of Endocrinology.

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Annales d'Endocrinologie
Annals of Endocrinology

Annales d'Endocrinologie 78 (2017) 54–69

Letter to the Editor

Hemorrhagic pheochromocytoma presenting as severe hypertension with myocardial infarction

Phéochromocytome hémorragique. Présentation clinique par hypertension artérielle sévère et infarctus du myocarde

1. Case report

A 50-year-old man, presented to the emergency department of our tertiary care hospital complaining of sudden right hypocondrial pain extending to the back, followed with an abrupt frontal-occipital cephalea and intense diaphoresis and nausea. He had no medical history of note except for being a smoker of 30 cigarettes a day. Over the last year, the patient's history was remarkable for intermittent episodes of cephalea, diaphoresis and palpitations lasting some minutes with spontaneous recovery, in a frequency of 3–4 times per week. They were not provoked by physical activity. There were not any records of blood pressure during the episodes. He did not undergo any diagnosis procedure since he did not consult any doctor before emergency admission. On arrival paramedics found him diaphoretic and tremolous, with heart rate of 110 beats per minute and blood pressure of 201/117 mmHg. ECG showed 2 mm ST-segment depression in leads II, III, aVF, and V4 to V6, consistent with inferior and lateral wall myocardial ischaemia. Paroxysms of ventricular tachycardia were controlled with intravenous nitroglycerin. The patient was treated initially with aspirin, clopidogrel, enoxaparin and urapidil. In the emergency department, chest radiography showed no evidence of acute cardiopulmonary disease. Initial laboratory work-up revealed elevated troponin-T of 1.16 ng/mL (normal < 0.04) with myoglobin of 211.9 ng/mL (normal < 70 ng/mL), elevated white cells count (37,700 mil/mm^3, normal 4–11 mil/mm^3), serum glycemia of 345 mg/dL (normal < 106 mg/dL) and haemoglobin of 15.1 g/dL (normal 13–17.4 g/dL). Contrast enhanced computed tomography scan of abdomen showed a right hemorrhagic adrenal mass. Antiplatelet and antitrombotic therapy was discontinued. The patient was transferred to the intensive care unit with the initial impression of myocardial infarction (MI) caused by hypertensive emergency and right adrenal hemorrhage. Over the next 24 hours, the patient's clinical status improved. Repeat laboratory results showed that his white blood cell count had fallen. Successive electrocardiograms showed the presence of asymmetrical peaked T waves in leads V_2 to V_4 with no ischemia signs or Q waves. Serum levels of troponin peaked at 24 hours (9.16 ng/mL) with myoglobin levels of 671 ng/mL. A transthoracic echocardiography performed 24 hours after the initiation of the symptoms revealed mild mitral regurgitation with a normal ejection fraction (70%). He was discharged from the intensive care unit three days later. Because of his medical history of headache and diaphoresis a 24-h urine collection for metanephrines was ordered. It returned with marked elevations in metanephrines (6,057 μg, normal < 374 μg), normetanephrines (1,218 μg, normal < 778 μg) and vanillylmandelic acid (23 mg, normal < 7.3 mg) levels. All the rest of the laboratory findings were normal. Both 123-I-metaiodobenzylguanidine scan and Single-Photon Emission Computed Tomography (SPECT) demonstrated a pathological uptake in the same location as the hemorrhage in the right adrenal gland (Fig. 1). On the basis of the clinical findings, laboratory reports and image procedures, the patient was suspected of having pheochromocytoma. Initially, cardiac angiography was not performed as it was strongly suspected that myocardial ischemia was secondary to the acute release of catecholamines from hemorrhagic pheochromocytoma. A decision was made to postpone the procedure after surgery except the patient experienced cardiac symptoms again. Before discharge the patient was started on aspirin. Because he maintained stable hemodynamic parameters, surgery was deferred to optimize preoperative adrenergic blockade. The patient was given oral doxazosin 4 mg for alpha-blockade for 2 weeks. Thereafter laparoscopic right adrenalectomy was performed successfully. During surgery, blood pressure was well controlled, although a few episodic rises required intravenous nitroglycerin. The patient was discharged home on the third postoperative day. The pathology report confirmed that the tumor was a pheochromocytoma with residual necrosis. At 2-month follow-up blood pressure remained normal off all medications. Metanephrine urine testing returned to within reference range. Eventually cardiac angiography was performed after surgery. It revealed no coronary atherosclerotic disease; left ventricular remained normal (ejection fraction 70%) and no mitral regurgitation was found. In view of these results, the final diagnosis was MI secondary to hemorrhagic pheochromocytoma and hypertensive emergency, with reversal myocardial ischiemia after tumor resection.

2. Discussion

Pheochromocytomas are rare cathecolamin-producing tumors derived from chromaffin cells of the adrenal medulla or

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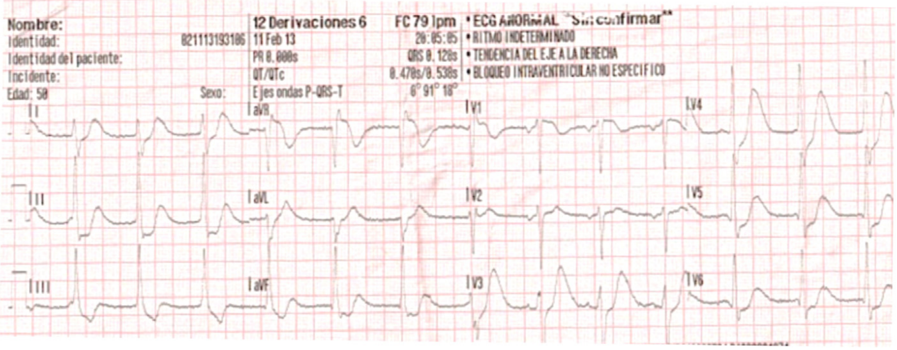

Nombre:
Identidad: 021113193106
Identidad del paciente:
Incidente:
Edad: 50 Sexo:

12 Derivaciones 6
11 Feb 13
PR 0.000s
QT/QTc
Ejes ondas P-QRS-T

FC 79 lpm
20:05:05
QRS 0.128s
0.470s/0.538s
6° 91° 18°

• ECG ANORMAL "Sin confirmar"
• RITMO INDETERMINADO
• TENDENCIA DEL EJE A LA DERECHA
• BLOQUEO INTRAVENTRICULAR NO ESPECIFICO

Fig. 1. Electrocardiogram on admission showing sinus rhythm with 2 mm ST-segment depression in leads II, III, aVF, and V4, V5, V6.

extra-adrenal paraganglioma. The classical triad symptom, is directly the consequence of the over secretion of catecholamines. It consists of palpitations, headaches and sweating lasting from minutes to hours, occurring episodically, and it is attended by hypertension [1]. Sustained or paroxysmal hypertension is commonly associated in 80–90% of patients with pheochromocytoma. Blood pressure can reach dangerously high values of over 200 mmHg in some patients as a consequence of the rapid and marked tumoral release of catecholamines, compromising the function of vital organs [2]. Some data have shown the relatively high incidence of cardiovascular complications in subjects with pheochromocytoma and concomitant hypertensive emergency [3]. MI and severe arrhythmia are among the most frequent heart complications. The specific association between pheochromocytoma and MI has been documented over many decades [4–6] and pheochromocytoma is associated with a wide variety of ischaemia-type ECG changes [4,5]. Monomorphic ventricular tachycardia and MI have been described as part of pheochromocytoma-induced cardiomyopathy [6]. Interestingly, most of these patients with myocardial ischemia, did not show coronary atherosclerosis in cardiac catheterization in contrast to classic atherosclerosis-mediated ischiemia [4,5]. For this reason, it is essential to rule out pheochromocytoma in an acute coronary syndrome presenting with hypertensive crisis and not relevant cardiovascular meal history. The increase routine use of echocardiogram has identified specific patterns of wall motion abnormalities in pheochromocytoma-induced cardiomyopathy similar to those reported in Takotsubo cardiomyopathy [4,7]. In our patient, the suspicion of pheochromocytoma-induced Takotsubo cardiomyopathy could not be confirmed and a formal diagnosis of MI was performed. Typical Takotsubo wall motion abnormalities were not present on echocardiogram. Moreover, the peak troponin level was 9 ng/mL. The critical value of troponin in Takotsubo cardiomyopathy has been reported to be as a mean 0.18 ng/mL [8], significantly less than that observed in MI. In general, a troponin level of more than 6 ng/mL is very likely to be associated to MI rather than to Takotsubo cardiomyopathy [9]. If there is clear evidence of myocardial ischemia, it is important to perform a prompt cardiac angiography. In our patient initially cardiac angiography was not initially performed because of hemodynamic instability and evidence of partially necrotic adrenal mass. A decision was made to postpone the procedure after the removal of pheochromocytoma when cardiac enzymes and ST-segment deviations normalised. However, this approach is debatable. Indeed, early diagnosis is mandatory to prevent severe cardiovascular complications in pheochromocytoma, since cardiac dysfunction is generally reversible after curative surgery [10].

Plasma free metanephrines or urinary fractionated metanephrines offer the highest sensitivity for diagnosis of pheochromocytoma [11]. In general, plasma concentrations of free normetanephrine higher than 430 μg/L or of free metanephrine higher than 220 μg/L unequivocally confirm a pheochromocytoma [9]. In those patients with clinical cardiomyopathy, plasma metanephrine levels are even substantially elevated. Therefore, if the metanephrine levels are normal or borderline, pheochromocytoma-induced cardiomyopathy can generally be ruled out [12]. Once the diagnosis of pheochromocytoma is considered, management must be initiated with fluid, and drug resuscitation and α-blockade. It is recommended that patients should not proceed to laparoscopic curative surgery unless they have been adequately treated with α-blockade for at least 10 days [1]. Urgent surgery is not indicated even in the presence of hemorrhagic pheochromocytoma because it has been shown that delayed surgery is associated with fewer intraoperative and postoperative complications but also with lower mortality rate [13].

Disclosure of interest

The authors declare that they have no competing interest.

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http://dx.doi.org/10.1016/j.ando.2016.10.004

Partial hypopituitarism in a female patient with a 45,X/46,XY mosaicism

Hypopituitarisme partiel chez une patiente avec un mosaïcisme 45,X/46,XY

1. Observation

A 20-year-old female patient was referred to our department for short stature and primary amenorrhea. She was the sixth child of a non-consanguineous marriage. Her past medical history was unremarkable. There were no physical complaints or symptoms.

On examination, she had a body weight of 44 kg, a height of 138 cm (<–4 standard deviations), a body mass index of 23.1 kg/m^2, a supine and standing blood pressure of 120/60 mmHg, a round face with a low posterior hairlines and multiple cutaneous nevi. She had a female phenotype with female external genitalia (Tanner stage: breast development: stage 3 and pubic hair: stage 2). Her bone age was delayed (< 17 years).

Laboratory tests revealed hypergonadotropic hypogonadism with FSH level of 115 mIU/mL (normal ranges: 3.35–21.63 mIU/mL), LH level of 38.33 mIU/mL (normal ranges: 2.39–6.6 mIU/mL) and estradiol level < 9 pg/mL (normal ranges: 18–147 pg/mL). Thyroid function and prolactin level were normal.

L dopa stimulating test showed growth hormone deficiency (peak GH = 3.89 ng/mL, normal response > 10 ng/mL) and insulin-induced hypoglycemia test confirmed this diagnosis (peak GH = 1.25 ng/mL, normal response > 10 ng/mL). IGF1 concentration was beyond the normal range (100 ng/mL, normal ranges: 220–850 ng/mL). The peak cortisol level in response to insulin-induced hypoglycemia test was 212 nmol/L (normal response > 550 nmol/L). ACTH level was lower than normal (< 10 pg/mL) indicated corticotropin deficiency.

Pelvic ultrasonography and magnetic resonance imaging (MRI) scan showed hypoplastic uterus with no visualized ovaries. MRI of the hypothalamic and pituitary region was normal. Echocardiography and renal sonography were normal. The bone mineral density showed osteoporosis.

Cytogenetic analysis of peripheral blood revealed a karyotype with mos 45,X[9]/46,XY[41].

Molecular analysis of *SRY* gene was positive.

Patient was treated with hydrocortisone. Growth hormone substitution therapy was prescribed but coverage has not been accepted by the national insurance system.

Laparoscopy showed apparently complete Müllerian structure with streak gonads. Because of the high risk of gonadoblastoma and dysgerminoma among subjects with 45,X/46,XY mosaicism, bilateral prophylactic gonadectomy was performed to our patient. Later, sex steroid replacement therapy was started.

2. Discussion

Turner syndrome is the most common chromosomal anomaly in females occurring in 1/2500 live born females. This syndrome is caused by a partial or complete absence of one sex chromosome. Out of all the patients diagnosed with Turner syndrome, about 2% to 5% are individuals with 45,X/46,XY [1]. In our country, the prevalence of 45,X/46,XY mosaicism among patients with Turner syndrome varies from 3% to 4.3% [2,3].

This extremely rare condition with an estimated incidence of 1.5/10,000 newborns is characterized by a wide phenotypic spectrum. In fact, patients with 45,X/46,XY mosaicism ranged from women with or without Turner syndrome stigmata, to men apparently normal, passing by the ambiguous phenotypes [4]. Such phenotype variability is thought to be related to the tissue distribution and relative proportions in the developing gonads of the respective cell lines, particularly those with functional copies of the *SRY* gene [5].

The most common presentation for individuals with a 45,X/46,XY karyotype is sexual ambiguity, accounting for ∼60%, and the least common phenotype consists of those with bilaterally descended testes, found in 11–12% [6].

Our patient presented with a phenotypically Turner-like female despite the small proportion of 45,X cells found in blood karyotype. In fact, mosaicism found in lymphocytes does not

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Table 1
Literature review of published cases of coexisting gonadal dysgenesis and GHD.

	Efstathiadou et al., 2000 [10]	Gallichio et al., 2003 [11]	Efthymiadou et al., 2012 [12]	Bougacha-Elleuch et al., 2016 [13]	Oueslati et al., 2016 [14]	Our current case
Age at diagnosis (years)	17	11	15	31	17	20
Height cm (SD)	126 (–6 SD)		141,5 (–3.55 SD)	136	130 (< –4 SD)	138 (< –4 SD)
Bone age (years)	12	8.8	13.5	–	14	< 17
Phenotype	Female	Female	Male	Female	Female	Female
Other pituitary deficiency	Thyrotropin and gonadotropin deficiencies	Thyrotropin and gonadotropin deficiencies	No	Thyrotropin and gonadotropin defeciencies	No	Corticotropin deficiency
Pituitary MRI	Hypoplastic pituitary + ectopic neurohypophysis	Empty sella turcica	ND	Empty sella turcica	Normal	Normal
Karyotype	45X	45,X/46,XX	45,X/46,XY	45,X/46,XX	45X	45,X/46,XY

GHD: growth hormone deficiency, SD: standard deviations, ND: not determinated.

reflect the proportion of gonadal mosaicism and is not correlated to the phenotype as previously reported [7,8].

Although 45,X/46,XY patients often present with short stature, growth hormone deficiency is not a common finding. Growth hormone deficiency likely does not occur in this disorder as confirmed by the normal GH response to stimulation tests [9]. Testing GH secretion was performed to our patient as she had a severe short stature.

Coexisting GH deficiency and gonadal dysgenesis was reported in few girls with Turner syndrome and in only one boy with 45,X/46,XY mosaicism (Table 1).

In addition to somatotropin deficiency, corticotropin deficiency was proven in our patient and the pituitary MRI was normal.

The first case of concomitant pituitary insufficiency and gonadal dysgenesis due to Turner syndrome was described by Efstathiadou [10]. At first, this patient was diagnosed with somatotropin, thyrotropin and gonadotropin deficiencies. According to a number of clinical characteristics and the absence of ovarian tissue on ultrasound, karyotype was performed. It revealed concurrent gonadal dysgenesis due to Turner syndrome with no evidence of mosaicism. Magnetic resonance imaging scan showed hypoplastic pituitary and ectopic localization of neurohypophysis [10].

In a recent study, Bougacha-Elleuch described for the first time 3 Tunisian sisters with Turner syndrome and hypopituitarism. Somatotropic insufficiency was proven in one case. In these patients, pituitary MRI has shown an empty sella turcica with hypoplastic pituitary gland [13]. Author had suggested common genetic background for the two diseases.

Congenital hypopituitarism induced by mutations of genes coding for transcription factors involved in pituitary development is a rare disease. A number of these genes have been identified in the recent years and include the transcription factors *HESX1, PROP1, POUF1, LHX3, LHX4, PITX1, OTX2, SOX2*, and *SOX3* [15]. Each gene acts in particular groups of cells. Therefore, various genetic mutations are associated with specific hormone deficiencies. Given its midline location, hypopituitarism is often associated with a wide spectrum of craniofacial and midline defects [16].

Our patient had GH and corticotropin deficiencies with normal MRI. The diagnosis of congenital hypopituitarism was suspected but no molecular analyses were performed. Deficiency of only GH and corticotropin hormones found in our patient was not previously reported and does not seem to be caused by mutation of any of the known genes. However, late onset of new pituitary deficiencies still possible and strict follow-up is required.

Up to date, only less than 15% of the aetiologies of congenital hypopituitarism have been identified [15]. Genetic investigation of our case may contribute to the identification of new causative gene which may be involved in both 45,X/46,XY mosaicism and hypopituitarism.

Our case represents a new illustration of the clinical heterogeneity of 45,X/46,XY mosaicism requiring a multidisciplinary evaluation and a long-term follow-up as recommended [17].

Disclosure of interest

The authors declare that they have no competing interest.

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Polycystic ovary syndrome: A new phenotype in mosaic variegated aneuploidy syndrome?

Syndrome des ovaires polykystiques : un nouveau phénotype du syndrome d'aneuploïdie en mosaïque ?

1. Clinical report

A 27-year-old woman with a history of short stature in infancy and oligo menorrhea presented with secondary amenorrhea. She was the product of a third pregnancy of non-consanguineous parents. She had no cognitive impairment. She had her menarche at the age of 12 years, since then she reported chronic menstrual irregularities. She has had secondary amenorrhea since twelve months. Physical examination showed a short neck without microcephaly, short stature with a height of 1.22 meters and a short proximal limb segments (Fig. 1). Her weight was 45 kg and body mass index 30 kg/m^2, with a waist circumference of 80 cm. Systolic blood pressure was 90 mmHg and diastolic blood pressure was 60 mmHg. She had a facial dysmorphia: temporal bossing, triangular face, hypertelorism and micrognathia. She had male pattern with a frontal baldness without hirsutism or other signs of virilism (Fig. 2). Skeletal abnormalities were knee varus, short fingers and toes, broad first toe and a wide sandal gap between the first and the second toes (Figs. 3 and 4).

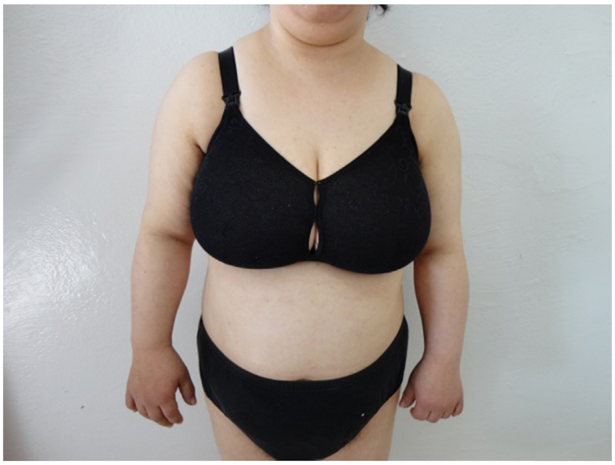


Fig. 1. Patient's morphotype: short stature short proximal limb segments.

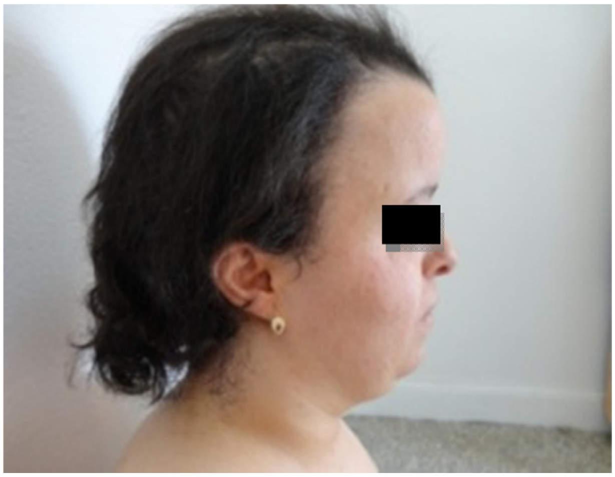
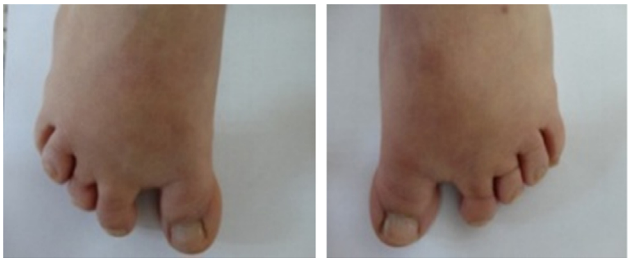


Fig. 2. Facial dysmorphia: short neck, temporal bossing, micrognathia.



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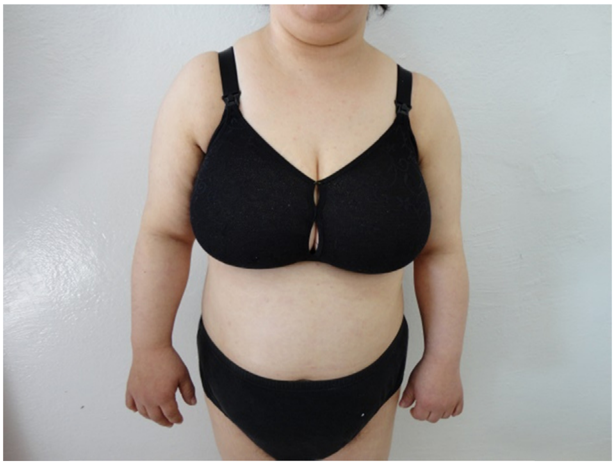

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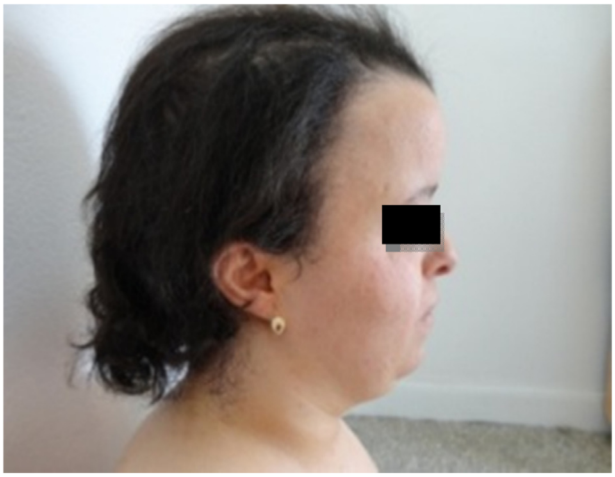

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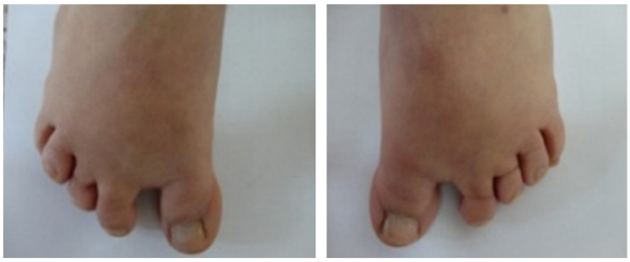

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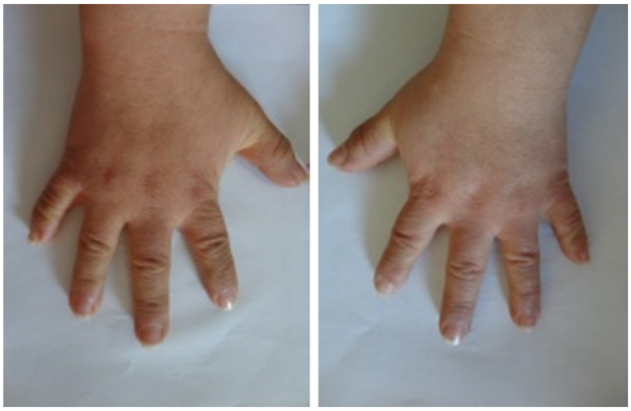


Fig. 4. Hand skeletal abnormalities: short fingers.

Table 1
Hormonal tests.

	Reference range	2010	2011	2012
FSH (UI/L)	1–20	4.8	9.3	
LH (UI/L)	2–20	4.7	7.5	
Estradiol (pg/mL)	39–189		20	84.2
Prolactin (ng/mL)	2–25	11	9	
FT4 (ng/dL)	0.71–1.85	1.32	1.14	
TSH UI/mL	0.12–3.4	1.86	2.48	
Cortisol baseline (μg/L)	42–384	110	215	
Testosterone (ng/mL)	0.1–0.58	0.75	1.05	
IGF-1 (μg/L)	108–247		187	

Table 2
Metabolic tests.

	Reference range	June 2011	November 2011
Fasting glucose (g/L)	0.7–1	1.15	
Plasmatic glucose 2 hours after OGTT[a]			3.44
Total cholesterol (g/L)	1.2–2	2.16	2.28
Triglyceride (g/L)	0.5–2	1.20	1.41
HDL cholesterol (g/L)	0.35–7	0.35	–

[a] OGTT: oral glucose tolerance test: the glucose cut-off for 2h-75 g OGTT was 2 g/L.

The pituitary hormone tests revealed normal baseline gonadotropin level. The progesterone withdrawal test was positive. The insulin tolerance test showed an insufficient GH response (5.3 ng/mL). IGF1 level was normal for age. Thyroid and adrenal hormones were normal. Testosterone level was moderately elevated (Table 1). The metabolic tests showed hypercholesterolemia, low HDL cholesterol and a type 2 diabetic status (Table 2). The pelvic ultrasonography revealed normal ovary volume: 6.7 mL on the right, 8.4 mL on the left and multiple follicles in both ovaries. Pituitary MRI revealed a hypoplastic anterior pituitary gland and a Rathke's cleft cyst (Figs. 5 and 6).

The initial peripheral blood chromosome study showed multiple and diverse aneuploidy in 20% of mitotic cells. The second showed aneuploidy in 30% of mitosis (Fig. 7).

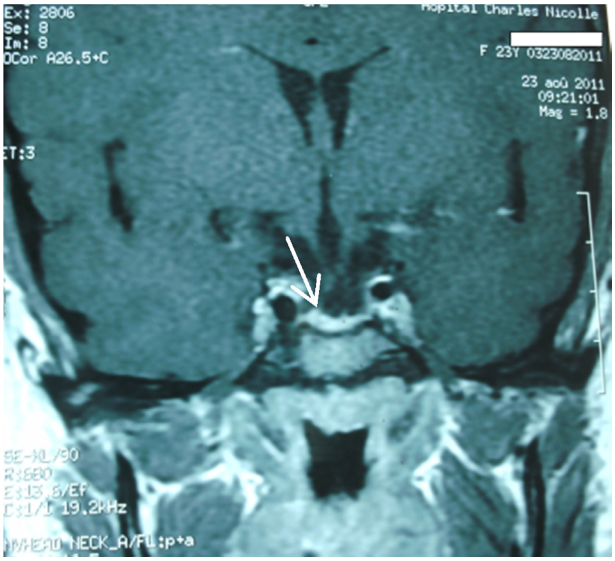


Fig. 5. Coronal MRI showing hypoplastic anterior pituitary.

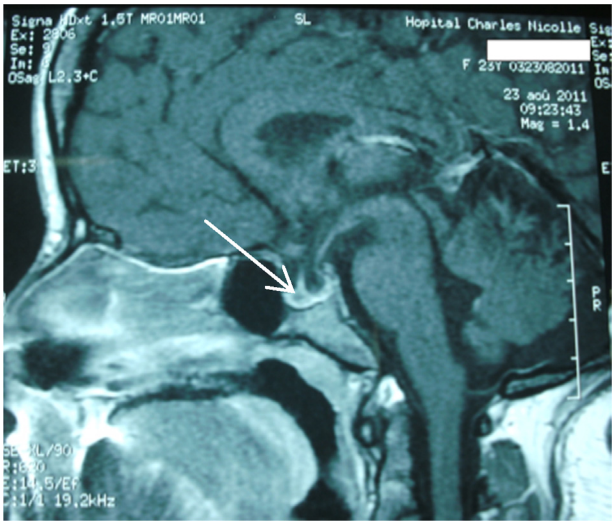


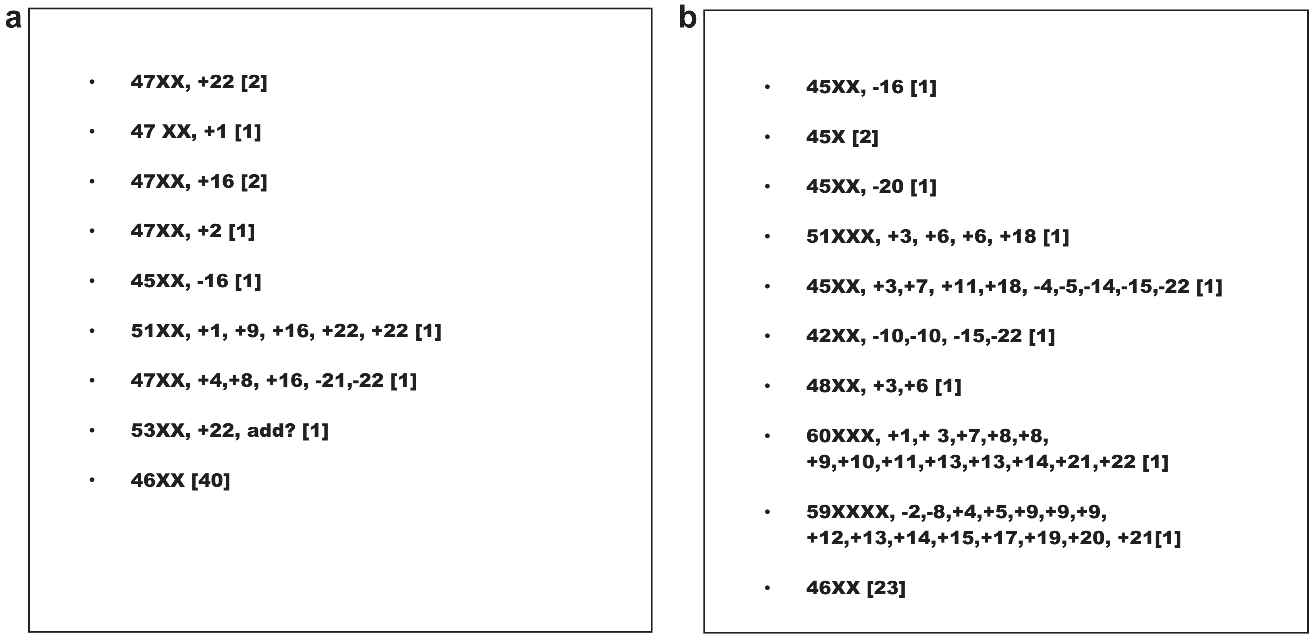
Fig. 6. Gadolinium-enhanced sagittal T1 MRI showing Rathke's cleft cyst (white arrow).

The screening for neoplasia was negative; full blood count was normal. Radiographs showed a normal bone squeletton, they did not show evidence for ovarian tumor. Abdominal pelvic ultrasound did not show evidence for ovarian tumor.

During 2 years follow-up, amenorrhea persisted but bleeding occurred whenever progestative therapy was used.

2. Discussion

Our case is the first report of metabolic syndrome and secondary amenorrhea in mosaic variegated aneuploidy syndrome (MVA). It is a very rare condition characterized by constitutional mosaic aneuploidies, non-specific phenotype including microcephaly, mild malformations, growth and mental retardation, and an increased risk of malignancy [1,2]. Dysmorphic



a

- 47XX, +22 [2]
- 47 XX, +1 [1]
- 47XX, +16 [2]
- 47XX, +2 [1]
- 45XX, -16 [1]
- 51XX, +1, +9, +16, +22, +22 [1]
- 47XX, +4,+8, +16, -21,-22 [1]
- 53XX, +22, add? [1]
- 46XX [40]

b

- 45XX, -16 [1]
- 45X [2]
- 45XX, -20 [1]
- 51XXX, +3, +6, +6, +18 [1]
- 45XX, +3,+7, +11,+18, -4,-5,-14,-15,-22 [1]
- 42XX, -10,-10, -15,-22 [1]
- 48XX, +3,+6 [1]
- 60XXX, +1,+ 3,+7,+8,+8, +9,+10,+11,+13,+13,+14,+21,+22 [1]
- 59XXXX, -2,-8,+4,+5,+9,+9,+9, +12,+13,+14,+15,+17,+19,+20, +21[1]
- 46XX [23]

Fig. 7. Blood chromosome study.

facial features in MVA syndrome are low-set ears, micrognathia, epicanthic folds, occipital prominence, broad nasal bridge, triangular face, frontal bossing and hypertelorism. Other neurological and eye abnormalities, skeletal hand and foot abnormalities and dermatological anomalies have also been described [3].

The diagnosis of MVA syndrome is based on the increased rate of variable aneuploidies in observed cells. The proportion of aneuploid cells in individuals with MVA is variable, but is usually more than 10% and substantially greater than in normal individuals [4]. The phenotype was mild in our patient, including craniofacial dysmorphic feature and growth retardation, genetic study showed predominantly nonosomies with multiple trisomy in blood lymphocyte. The oligomenorrhea lets us discuss different diagnosis. The direct relationship between hypoplasic pituitary and secondary hypogonadism was less plausible as the lack of gonadotropin has not been described in MVA syndrome before and the progesterone withdrawal test was positive in our patient. Hormonal deficiencies have not been described in previous reports of MVA, although a few cases suggested this possibility [5]. Short stature is not specific of MVA syndrome; it can be related to GH deficiency as reported in some rare cases or to skeletal abnormalities [6]. Pituitary tests in our patient demonstrated a modest GH secretory response to stimulation and a normal IGF1 level, suggesting a partial GH deficiency. Oligomenorrhea in our patient may be related to the high testosterone level that is strongly suggesting a polycystic ovary syndrome (PCOS). However, the antral follicular count and follicular size were not mentioned in suprapubic pelvic ultrasound. So transvaginal ultrasound criteria for PCOS were missed. Short stature, high testosterone and amenorrhea can be also observed in congenital adrenal hyperplasia. Unfortunately, 17OH-progesterone level could not be measured in our patient. Therefore 21-hydroxylase deficiency is not ruled out. Plagia et al. previously described a case of MVA syndrome in a girl who had primary amenorrhea with normal secondary characteristics in addition to mental retardation, microcephaly and short stature. Variegated aneuploidy related to premature centromere division was found [7]. Our patient had also metabolic syndrome as she had obesity, low HDL cholesterol and diabetes mellitus. Metabolic abnormalities have not been described previously in MVA syndrome. These metabolic disorders could be related to the PCOS. One case of obesity with MVA syndrome has been published [8].

Common tumors reported in MVA syndrome are Wilms tumour, rhabdomyosarcoma, leukaemia and granulosa cell tumor of the ovary [1]. MVA patient with BUB1B mutation are different regarding the risk of cancer. In fact, except leukemia, malignancy risk seems to be related to *BUB1B* mutation. The age of tumor diagnosis varied and ranged between nine weeks and seven years in most cases [9]. However, our patient was 27 years old and no cancer was found.

3. Conclusion

The phenotype of our patient was not specific. This case reported the first case of MVA syndrome that associates secondary amenorrhea and metabolic abnormalities. Additional features mimicking PCOS may occur in MVA syndrome.

Consent statement

Informed consent was obtained from the patient for publication of the case report and accompanying images.

Disclosure of interest

F. Chaker, M. Chihaoui, M. Yazidi, O. Rejeb, S. Neji, H. Kraoua declare that they have no competing interest.

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http://dx.doi.org/10.1016/j.ando.2016.08.002

Fetal hypothyroidism induced by maternal anti-TSH receptor blocking antibodies and complicated by polyhydramnios despite the absence of goiter. Treatment by intra-amniotic injections of levothyroxine

Hypothyroïdie fœtale induite par des anticorps bloquants anti-récepteur de la TSH d'origine maternelle, compliquée de polyhydramnios malgré l'absence de goitre. Traitement par injection intra-amniotique de levothyroxine

1. Case report

A 33-year-old young woman starting her first pregnancy had a history of hypothyroidism since her teenage years, due to an auto-immune chronic thyroiditis with a hypoplastic thyroid and high levels (200 UI/L) of TSH-receptor antibodies (TRAb) with more than 80% thyroid blocking antibody activity. She was treated with levothyroxine 150 μg/day resulting in a normal TSH (0.5 mUI/L).

Given the potential fetal consequences of the maternal thyroid disease a close multidisciplinary monitoring (obstetrician, sonographist, endocrinologist) was initiated. At 16 weeks of gestation (WG), TRAb levels were 350 UI/L with 86% blocking activity, TSH 0.345 mUI/L (N: 0.17–4.23 mUI/L) and FT4 23 pmol/L (N: 12–22 pmol/L). The ultrasonographies at 18 and 25 WG found no abnormal morphological elements, but femoral length was at the 10th percentile. At 33 WG the mother maintained a normal TSH (0.873 mUI/L) and FT4 (16.5 pmol/L). Ultrasound monitoring showed a polyhydramnios (vertical dimension of the largest pocket of amniotic fluid: 10 cm) and a delay in bone maturation: absence of femoral epiphyseal ossification, with a femoral length still at the 10th percentile while cephalic and abdominal biometrics were at the 50th percentile. There was no gestational diabetes. Fetal hypothyroidism was suspected and the case was presented at the Multidisciplinary Committee of Prenatal Diagnosis of University Hospital in Grenoble. The advice of the committee was to perform amnio-reduction for the following objectives: drainage of polyhydramnios to avoid pregnancy complications; determination of fetal karyotype; evaluation of fetal thyroid function by measurement of thyroid hormones and TRAb in the amniotic fluid; and finally injection of 200 μg levothyroxine after amniotic reduction.

The procedure was carried out at 34 WG + 4 days without difficulty allowing a drainage of 1000 mL amniotic fluid. Amniotic TSH was elevated: 4.36 mUI/L (N: 0.04–0.51 mUI/L) while FT4 was undetectable (< 2.4 pmol/L); TRAb were very high at 67.40 UI/L (54% of stimulating TRAb, > 80% of blocking TRAb). Normal values are those published in 2007 [1].

This allowed to confirm fetal hypothyroidism linked to transplacental transfer of maternal TRAb and it was decided to carry out new intra-amniotic injections of levothyroxine weekly until childbirth, with monitoring of the treatment on amniotic hormones levels (Fig. 1). Because the first injection lead to normalization of amniotic levels of FT4 and FT3, the same dosage of levothyroxine (200 μg) was used at each injection. Successive ultrasound examinations showed no recurrence of

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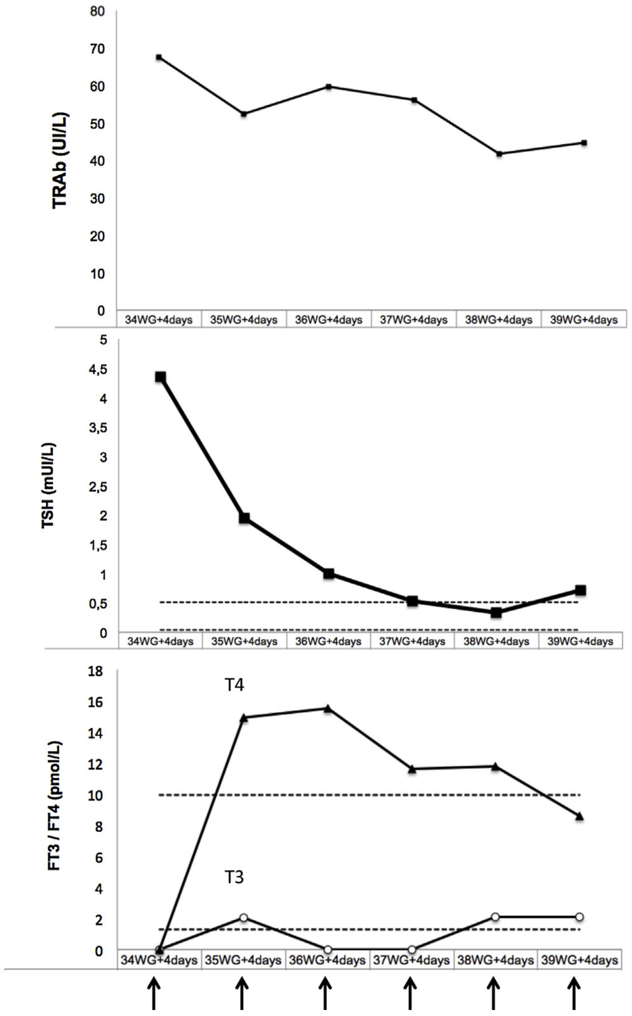

Fig. 1. Evolution of amniotic levels of TRAb, TSH, fT4 and FT3 before and during treatment by weekly intra-amniotic injection of 200 μg levothyroxine. There is a difference between the chemical composition of the standard solutions used for assay calibration and that of the biological medium containing the amniotic fluid to be assayed. The validation of measurement of TSH, FT3, FT4 and TRAb in amniotic fluid have been realized by using a solution with bovine serum albumin (BSA) to approximate protein concentrations in serum.

polyhydramnios, but the distal femoral ossification center was still absent at 36 WG.

A normal labor and delivery lead to birth at 40 WG + 1 day (4 days after the last injection of levothyroxine) of a boy with a mild hypotrophy: birth weight 2710 g (5th percentile), size 47 cm (5th percentile), head circumference 35 cm (50th percentile). There was no goiter. Apgar score was 10/10/10; there was a mild bradycardy (heart rate between 90 to 120 bpm) during the first 3 hours of life and a slightly low body temperature (between 35.5 °C and 36.5 °C) during the first 12 hours of life, requiring the set up of a radiant warmer during 36 hours.

Breast-feeding was not desired by the mother, infant formula was well tolerated, passage of meconium not delayed, no mucocutaneous jaundice. At birth, cord blood tests show a high TSH level (65 mUI/L), a normal FT4 (16 pmol/L) but a low FT3 (< 2 pmol/L), very high TRAb (1593 UI/L, with 94% blocking activity), indicative of a moderate hypothyroidism linked to transplacental transfer of maternal TRAb. Maternal TSH at delivery was normal at 1.2 mUI/L.

Oral substitutive therapy of the neonate was initiated at 17 hrs of life with 9 μg/kg/day of levothyroxine. Substitutive therapy was monitored on TSH and FT4 measurements and had to be pursued for 5 months, until disappearance of TRAb.

2. Discussion

In this case report fetal hypothyroidism was suspected despite the absence of goiter because we knew the mother had high levels of TRAb with blocking activity, which may cross the placenta and inhibit fetal thyroid function. Indeed the placental transfer of TRAb and the inhibition of fetal thyroid were confirmed by measurements in the amniotic fluid of high TRAb, low T4 and high TSH levels. As expected, inhibition of thyroid function was persistent in the neonate, who required levothyroxine treatment until disappearance of maternal antibodies.

Fetal hypothyroidism was only suspected at 33 WG, with the appearance of a polyhydramnios, despite the absence of goiter, and the lack of distal femoral ossification center suggesting bone maturation delay, as 95% of the fetuses show the distal femoral ossification center at 32 WG [2,3]. It is interesting to note that polyhydramnios in fetal hypothyroidism is generally believed to be related to the compression of the goiter on the esophagus, resulting in decreased fetal ingestion of amniotic fluid [4]. However, our observation and others [5] suggest that there are other mechanisms that can lead to polyhydramnios in fetal hypothyroidism.

Suspicion of hypothyroidism opened a discussion regarding the interest of in utero treatment. Intra-amniotic therapy with levothyroxine has so far only been reported in hypothyroid fetuses with goiter, with the objective to prevent goiter related dystocia [6]. The interest of intra-amniotic replacement therapy with levothyroxine in the absence of a goiter may be debated since the fetal brain is believed to be relatively protected from defective fetal thyroid hormone production, not only through the placental transfer of maternal FT4 but also from up-regulation of brain type 2 deiodinase, which converts T4 into T3 [4]. Moreover, it is generally accepted that post natal levothyroxine substitutive therapy, started in the first two weeks of life allows a normal development even in neonates with thyroid agenesis, who are characterized with the absence of any production of FT4 during their entire fetus life. However, there is some evidence that this may not be entirely true, as several publications report that around 10% of neonates with thyroid agenesis have a mental development lower than normal despite early neonatal treatment [7–10]. This suggests that some consequences of severe fetal hypothyroidism are not compensated by postnatal substitutive therapy, but might be compensated by a treatment started earlier, in utero.

In this patient as polyhydramnios required amnio-reduction by amniotic puncture we decided, after discussion with the ethic committee, to take the opportunity of the amniotic puncture to take a sample for measurement of thyroid hormones and inject at least one dose of 200 μg levothyroxine in the remaining amniotic fluid. In the amniotic fluid FT4 level proved to be below detection limit while TSH was above the normal range, confirming fetal hypothyroidism and giving a rationale for intra-amniotic substitutive therapy.

In the different reports of intra-amniotic substitutive therapy for fetus with hypothyroidism associated with goiter the published dosage in levothyroxine ranged from 200 to 800 μg per injection, the number of injections from one to six, and the interval between injections from 1 to 4 weeks [6]. The majority of centers used 250 ± 50 μg per week, equivalent to 10 μg/kg, with fetal weight estimated by ultrasonography. This variability reflects the lack of consensus treatment guidelines. In this case 200 μg per week was decided somewhat arbitrarily until birth, however because the injections resulted in normalization of amniotic levels of FT4 and TSH from 34 to 39 WG, and because neonatal cord values measured 4 days after the last injection showed only slight neonatal hypothyroidism (elevated TSH, but normal FT3 and FT4) we believe 200 μg per week of levothyroxine was close to providing the appropriate amount of levothyroxine. Of note comparison of amniotic (39 WG + 4 days) and umbilical cord (41 WG + 1 day) levels of T4, TSH is not straightforward as they are separated by 4 days and an injection of 200 μg levothyroxine but suggest that only a fraction of these hormone is excreted in the amniotic fluid, whereas comparison of TSH receptor antibodies is more easy and allows to calculate that amniotic levels of these receptors is 3% the level of serum levels.

The clinical benefits of levothyroxine intra-amniotic treatment in this case can be discussed: the absence of polyhydramnios recurrence suggests a favorable therapeutic effect. On the other hand the fact that distal femoral ossification center was still not visible at 36 WG, and that the newborn was slightly hypotrophic at birth, might suggest that the supposed consequences of fetal hypothyroidism were not entirely reversed by the treatment, either because the supplementation in levothyroxine was too low or because it was not started early enough. The other hypothesis is that the femoral ossification defect, or the hypotrophy, were not linked to hypothyroidism. It is interesting to note that Ribaut and al., reported similar findings with all their 12 babies with hypothyroidism diagnosed at birth despite very different treatment protocols and the normalization of TSH level in amniotic fluid [6]. These authors therefore conclude that intra-amniotic TSH levels may not be reliable enough to assess fetal thyroid status and that intervals of 1–6 weeks between intra-amniotic injections may be too long.

In conclusion in this case report fetal hypothyroidism linked to TRAb was responsible for very low amniotic levels of FT4 and FT3 and was associated with a femoral ossification defect and with polyhydramnios despite the absence of goiter. Intra-amniotic treatment by levothyroxine restored normal levels of amniotic T4, and there was no recurrence of polyhydramnios. We believe this observation allows raising the question of the interest of intra utero treatment of hypothyroidism even when the fetus has no goiter. This question might even be relevant to athyreotic fetus if the development of fetal sonography allows to a prenatal diagnostic of the absence of a thyroid gland. It should be remembered that although it has been reported that there is some maternal-fetal transfer of thyroxine in fetus with severe hypothyroidism [11] it has been demonstrated that this transfer does not suffice to prevent the effects of in utero hypothyroidism [12].

Disclosure of interest

The authors declare that they have no competing interest.

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http://dx.doi.org/10.1016/j.ando.2016.09.002

Choroidal metastasis from papillary thyroid cancer: An unusual feature of a common disease

Métastase choroïdienne d'un carcinome papillaire thyroïdien : une manifestation inhabituelle d'une maladie fréquente

1. Case presentation

A 49-year-old female with a multinodular goitre underwent total thyroidectomy and central neck dissection. Pathology revealed two foci of papillary thyroid cancer (PTC) with follicular architecture. The largest measuring 1.5 cm was located in the right thyroid lobe, while in the left lobe, a 0.15-cm microcarcinoma was identified. There was invasion of the thyroid capsule from the right lobe cancerous nodule, with extension to the perithyroid adipose tissue, and lymph node metastases in the central neck compartment. There was no vascular invasion or evidence of aggressive histology (such as tall cell, hobnail variant or columnar cell carcinoma).

Two months after thyroidectomy, the patient received radioactive iodine (RAI) therapy (100 mCi). Her TSH stimulated thyroglobulin (TG) at the time of ablation was considerably elevated at 196 ng/mL, but associated to the presence of circulatin TG-antibodies. Post-treatment whole body scan revealed activity in the thyroid bed and no extrathyroidal uptake. At this time, the patient's PTC was classified as stage III, T3N1aM0.

Three months later, TG levels remained elevated at 289 ng/mL (< 1 ng/mL) on thyroid hormone suppression and follow-up ultrasonography showed suspicious lymph nodes at the right side of the neck. Chest computed tomography (CT) revealed multiple lung metastases bilaterally. Subsequently, the patient underwent lymph node dissection of the right neck region and a second course of RAI treatment was scheduled. Pathology findings were consistent with metastatic PTC, as 6 out of the 15 excised lymph nodes were infiltrated.

Prior to the second RAI treatment, stimulated TG was grossly elevated at 9970 ng/mL, with undetectable, TG antibodies. Following administration of 150 mCi of ^{131}I, whole-body scintigraphy showed no residual activity in the thyroid bed but multiple spots in both lungs.

Despite this treatment, TG levels did not decline, so a third dose of ^{131}I (150 mCi) was administered 6 months later. The post-treatment scan showed multiple new foci of increased activity in both lungs and especially in the right middle and lower lobe. Additionally, new ^{131}I uptake at the head of right femoral neck was identified.

Further investigations with CT scanning of her chest and abdomen, as well as a technetium-99 m (^{99m}Tc) bone scan, revealed the presence of metastatic lesions in the lungs, mediastinum, and right femoral head. Given the high risk of femoral fracture, the patient underwent intramedullary nailing and external beam radiation therapy. Due to disease progression, off label systemic treatment with the tyrosine kinase inhibitor (TKI) sorafenib was initiated, at a dose of 800 mg daily.

Given the iodine-avid lung and bone metastases, as shown by the post-iodine treatment scans, the patient received a fourth dose of ^{131}I (150 mCi). This time the post-treatment scan revealed, apart from the already known lung, femoral bone, and mediastinum lymph node metastases, increased activity in the right neck region, due to infiltrated lymph nodes, as confirmed by neck ultrasound.

The disease was stable for a period of 12 months, with TG levels ranging between 4000–5000 ng/mL on thyroid hormone suppressive therapy and sorafenib treatment. However, the patient experienced many TKI-related side effects, in particular diarrhea and hand-foot syndrome, which persisted despite dose reductions. Inevitably, there were periods when the patient was not receiving the TKI in order for the side effects to subside.

Three years after the initial diagnosis, the patient complained of blurred vision. Fundoscopy revealed an orange-yellow choroidal mass with hemorrhagic retinal detachment in the posterior pole temporal to the macula of the right eye (Fig. 1a). B-mode ultrasonography of the eye showed a solid mass, without any significant reduction of reflectivity in its interior, an echographic finding characteristic of choroidal metastasis (Fig. 1b). Further investigations with CT scanning of her neck, chest, and abdomen, as well as orbital magnetic resonance imaging (MRI), revealed an increase in the size and number of the lung metastases, mediastinum and cervical lymph nodes as well as a mass lesion measuring 7.6 × 6.5 mm, at the temporal side of the right eye that caused a small detachment and bleeding of the retina (Fig. 1c).

The choroidal lesion was not evident by whole body ^{131}I scintigraphy after rhTSH stimulation, whereas there was a significant rise of TG levels (Tg: 32700 ng/mL). At this stage, sorafenib was discontinued and therapy with sunitinib 37.5 mg od was initiated.

However, the tumor of the right eye progressed rapidly despite systemic therapy with sunitinib as well as intravitreal

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http://dx.doi.org/10.1016/j.ando.2016.09.002

Choroidal metastasis from papillary thyroid cancer: An unusual feature of a common disease

Métastase choroïdienne d'un carcinome papillaire thyroïdien : une manifestation inhabituelle d'une maladie fréquente

1. Case presentation

A 49-year-old female with a multinodular goitre underwent total thyroidectomy and central neck dissection. Pathology revealed two foci of papillary thyroid cancer (PTC) with follicular architecture. The largest measuring 1.5 cm was located in the right thyroid lobe, while in the left lobe, a 0.15-cm microcarcinoma was identified. There was invasion of the thyroid capsule from the right lobe cancerous nodule, with extension to the perithyroid adipose tissue, and lymph node metastases in the central neck compartment. There was no vascular invasion or evidence of aggressive histology (such as tall cell, hobnail variant or columnar cell carcinoma).

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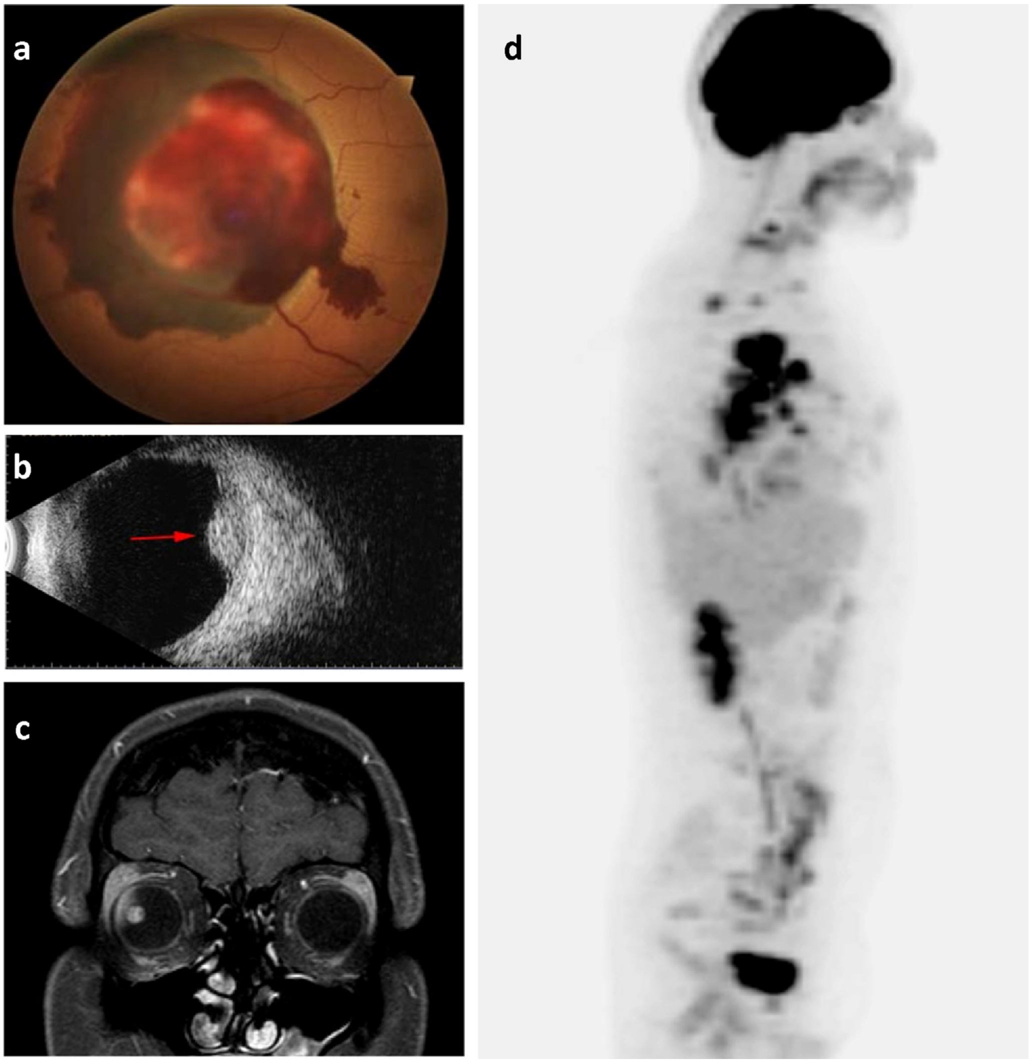

Fig. 1. a: fundoscopy showing an orange-yellow choroidal mass with hemorrhagic retinal detachment in the posterior pole temporal to the macula of the right eye; b: B-mode ultrasonography revealing a solid mass (arrow) without any significant reduction of reflectivity in its interior: c: T1 magnetic resonance weighted image after gadolinium enhancement showing a 7.6 × 6.5 mm mass at the temporal side of the right eye that causes a small detachment and bleeding of the retina; d: fludeoxyglucose positron emission tomography/computer tomography revealing multiple metastatic lesions in bones, lungs, mediastinal and cervical lymph nodes, and at the right eye.

bevacizumab treatment, resulting in a total exudative retinal detachment and subsequent neovascular glaucoma.

On routine follow-up, 3 months later, the patient underwent a fludeoxyglucose positron emission tomography/computer tomography (FDG PET/CT) scan which showed multiple lesions in bones, lungs, mediastinal and cervical lymph nodes, and at the right eye (Fig. 1d). TG levels remained high (Tg: 12500 ng/mL) and she was submitted to external beam radiation therapy to the cervical and lumbar spine.

2. Discussion

We describe a patient with widespread stage IV, T3N1bM1, PTC (lymph node, bone, lung, brain, and liver metastases), presenting with a symptomatic choroidal metastasis 3 years after initial diagnosis.

Owing to its abundant vascular supply, the choroid is the most common ocular site for metastatic disease, most commonly arising from breast and lung cancer and less frequently from prostate, kidney, and gastrointestinal tract tumors [1].

Among the rare thyroid cancer cases with metastases to the choroid reported in the literature, the majority ($n = 9$) derive from papillary cancers, whereas follicular and medullary cancers with choroidal metastasis are even rarer ($n = 7$ and 6 respectively) [2–7]. They are found at an advanced stage of thyroid cancer and usually in RAI-refractory disease. Up till now, uptake of ^{131}I in the choroidal metastasis of differentiated thyroid cancer (DTC) has been reported in 6 out of a total of 18 patients (33%) [2,4–7].

Our patient complained of blurred vision 3 years after initial presentation. Indeed, impaired vision is the commonest symptom of a choroidal metastasis especially when it involves the optic nerve or macula. When the lesion is associated with an overlying retinal detachment, the patient may complain of flashing lights and floaters. In a small percentage of cases, patients with choroidal metastasis are asymptomatic [8].

Diagnosis is usually based on clinical examination and imaging modalities like MRI and ultrasonography. In our patient, fundoscopy revealed an orange-yellow choroidal mass, as usually found in thyroid, but also renal and carcinoid metastases, in contrast with metastases of other types of primary tumors that typically appear pale yellow in color [7,8]. Transretinal choroidal biopsy of the tumor, a procedure that carries a risk of endophthalmitis, is required only when the metastasis presents as the initial manifestation of a malignancy [5].

Our patient had RAI-refractory PTC as evidenced by:

- the presence of disease progression following multiple courses of RAI treatment, despite the fact that after each course there was ^{131}I activity on the post treatment scan;
- the concentration of RAI by some but not all metastatic lesions.

The choroidal lesion did not concentrate RAI and therefore was detectable by PET/CT and MRI but not by whole body ^{131}I scan. Given that most therapeutic options had failed (systemic treatment, intravitreal bevacizumab), the lesion was non RAI-avid and the patient had definite loss of vision along with severe pain, and therefore, enucleation was scheduled.

Treatment options of choroidal metastases secondary to DTC include ^{131}I therapy for RAI-avid lesions, with generally good results as indicated by previous cases [5–7]. External beam radiation that is commonly used in the treatment of choroidal metastases of other primary tumors has been effective in up to 60% of the cases of RAI-refractory disease [5,9]. Other therapeutic choices include brachyradiotherapy using ^{125}I episcleral radioactive plaque insertion and chemotherapy, with poor however outcomes [5]. Enucleation has been used for choroidal metastases that cause a definitive loss of vision or persistent pain [5]. Finally, intravitreal bevacizumab, a recombinant humanized antibody against vascular endothelium growth factor-A has been used in the last few years in the treatment of choroidal metastases by various types of cancer [10,11].

It appears that PTC is a heterogeneous disease, as recently demonstrated by molecular characterization [12], incorporating not only the common form that carries an excellent prognosis, but also some genuinely aggressive types of PTC, demonstrating rapid disease progression, de-differentiation and resistance to RAI therapy. The fact that RAI-refractory DTC is associated with poor prognosis and distant metastases [13] has stimulated research on agents that could enhance iodine accumulation in metastatic lesions. Up to now, the development of mTOR, BRAF and MEK inhibitors has been related with encouraging results on re-differentiating RAI-refractory DTC [14,15]. Additional studies are needed on the use of these agents that may benefit patients with non RAI-avid choroidal metastatic masses, rendering ^{131}I therapy potentially effective.

Disclosure of interest

The authors declare that they have no competing interest.

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http://dx.doi.org/10.1016/j.ando.2016.09.001

Early progression under mitotane and polychemotherapy does not mean failure in adrenocortical carcinoma patient

Une progression précoce sous mitotane et polychimiothérapie n'est pas synonyme d'échec chez les patients porteurs de corticosurrénalome

1. Case description

A 52-year-old female underwent surgery in March 2009 for a localized non-secretory adrenocortical carcinoma (ACC) of 17 cm. A Weiss score of 9 with a mitotic rate of more than 5/50HPF and a Ki67 of 10% were reported at pathology. Baseline imaging work-up showed pulmonary micronodules, hepatic and bones metastases and peritoneal carcinomatosis (Fig. 1A). Mitotane therapy was started in April 2009, with carboplatin-etoposide (MPE) because of pejorative prognostic factors. Response to treatment was evaluated every 2 months with CT based on RECIST 1.0 criteria and mitotane plasma level was monitored monthly (Fig. 1). The therapeutic window of mitotane plasma level was reached with a daily dose of 3 g/day 4 months after treatment initiation. Furthermore, a peak of 20 mg/L was reached twice on month 4 (19.2 mg/L) and on month 5 (20.6 mg/L). Along with that mitotane levels, a progressive disease was found until month 6 evaluation (Fig. 1B–D). Imaging work-up performed at month 8 after 6 cycles of EP and 2 cycles of carboplatin-etoposide found a stable disease and only mitotane was continued and decreased due to side effects at maximum tolerated dose. Locoregional approaches to treat the symptomatic bones metastasis were performed at month 10 (cimentoplasty, osteosynthesis and cryotherapy). A tumor response (hepatic partial response and pulmonary complete response) was observed for the first time 10 months after MEP initiation, 2 months after the end of carboplatin-etoposide and 6 months after mitotane peak was reached (Fig. 1F). Under mitotane alone, tumor response lasted 21 months after treatment initiation (Fig. 1G and H). At this time, because of progression in hepatic targets concomitant with a plasma mitotane level above 14 mg/L, radiofrequency was performed, making RECIST criteria not usable anymore on the liver while bone metastases were all treated with loco-regional approaches. Since 2010, the disease of this patient is still under control with the same strategy (locoregional approaches and mitotane) and a survival of more than 6 years after initial stage IV diagnosis.

2. Discussion

Adrenocortical carcinoma (ACC) prognosis is characterized by a 5-year survival of less than 15% at metastatic stage. Mitotane (o,p'DDD), an insecticide-derivative, is the only drug approved in advanced ACC either as monotherapy or combined polychemotherapy according to prognostic features [1]. Although targeting 14 to 20 mg/L, therapeutic plasma level window of mitotane is recommended [2], the time at which mitotane antitumor efficacy should be evaluated remains ill-defined. As a consequence, resistance to mitotane therapy is still not precisely defined and a significant number of ACC patients remains on mitotane therapy lifelong hampering proper evaluation of new therapeutic options. On the other hand, mitotane might be stopped too early in patients because of progression who could benefit from this therapy for prolonged period of time. We report here the case of a patient presenting with a stage IV ACC whose prolonged partial response was evidenced 6 months after mitotane level peak reached 14 mg/L after several tumor progressive status evaluations.

In medical oncology, demonstration of tumor progression challenges the continuation of the ongoing option. This clinical case illustrates a stage-IV bad prognostic ACC patient according the mENSAT-GRAS criteria [3], managed with polychemotherapy including mitotane, who turned into a long-term survivor thanks to a maintained partial response. Because partial response was first obtained at month 10, 2 months after EP regimen withdrawal and maintained for more than 6 years, we classified that response as due to mitotane therapy. However, we cannot eliminate a role of combined cytotoxic chemotherapy. Indeed, delayed response has not been described with cytotoxic chemotherapy alone whereas delayed antitumor activity is a well-known characteristic of mitotane, best demonstrated by the delayed time of several months needed to reach plasma therapeutic level in ACC patients [4]. Although, higher response rate and survival has been reported when plasma mitotane reached 14 mg/L, the kinetic of tumor response according to plasma mitotane level curve has never been reported. This case allows us to raise the hypothesis that the antitumor evaluation of mitotane therapy should be evaluated after the peak of plasma mitotane has been reached. In this case, plasma mitotane levels of 20 mg/L have been reached two times prior the demonstration of a long lasting partial response. From that date forth, plasma mitotane level was retrieved higher that 10, 14 or 20 mg/L out of 3, 3 or 1 measurements before the first demonstration of progression was evidenced. Recent literature on mitotane has suggested that both very high plasma mitotane levels above 20 mg/L and maintenance of therapeutic level were associated with better response rates and recurrence free survival [5,6]. In oncology, complete responses to chemotherapy or targeted agents are rare and various mechanisms of resistance have been proposed to explain reprogression. Targeting microenvironment rather than the tumor itself has been proposed to escape redundant pathway mechanisms of resistance. Antiangiogenic agents or immunotherapy have emerged as a promising application of such paradigm and unusual features of pseudoprogression have been described [7]. Mitotane has unique metabolic properties. Indeed, due to its lipophilic nature, plasma mitotane has been shown to mainly reflect lipoprotein binding [4]. In addition, recent publication has favored a direct intracellular mitochondrial targeting [8,9]. Finally, alteration of intracellular lipid profile as characterized by an increase in free cholesterol has been demonstrated and sterol O-acyltransferase 1 (SOAT1) proposed as the main target [10]. In the light of these observations, we hypothesize that the unique profile of delayed tumor response reported in this patient may resemble pseudo progression described in patients treated with immunotherapy

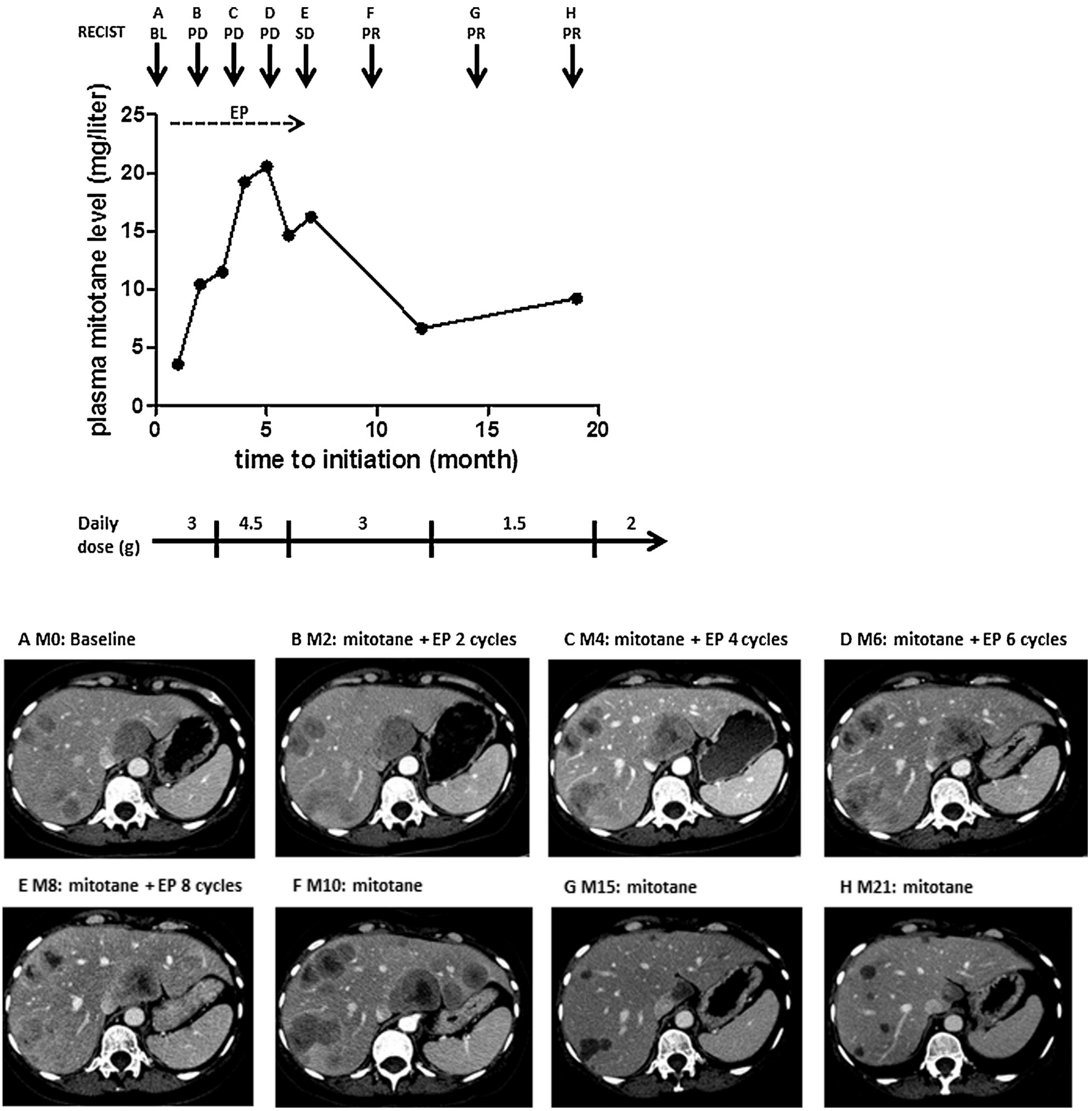
RECIST
A BL
B PD
C PD
D PD
E SD
F PR
G PR
H PR
EP
plasma mitotane level (mg/liter)
0
5
10
15
20
25
time to initiation (month)
Daily dose (g)
3
4.5
3
1.5
2
A M0: Baseline
B M2: mitotane + EP 2 cycles
C M4: mitotane + EP 4 cycles
D M6: mitotane + EP 6 cycles
E M8: mitotane + EP 8 cycles
F M10: mitotane
G M15: mitotane
H M21: mitotane

Fig. 1. Plasma mitotane levels (mg/L) versus time (month) with RECIST evaluations and daily dose of mitotane (g). Computed tomography scan results of the patient showing hepatic targets at baseline (A) and after 2 to 21 months after systemic treatment initiation (B to H). PD: progressive disease; SD: stable disease; PR: partial response; EP: etoposide + platine-based chemotherapy.

and, may reflect profound lipid metabolism targeting alteration induced by mitotane in the plasma and tumor cells of ACC patients. Mitotane could be maintained as long as it is well tolerated or effective but discussed in patients who cannot reach 8–10 mg [6].

In conclusion, we suggest that antitumor evaluation of mitotane therapy should be performed after at least one peak of mitotane. Retrospective and prospective studies are ongoing to confirm that result and the role of combined cytotoxic chemotherapy. Metabolomic targeting is proposed as an explanation of this unique profile of tumor response kinetic.

Disclosure of interest

The authors declare that they have no competing interest.

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http://dx.doi.org/10.1016/j.ando.2016.10.001

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Annales d'Endocrinologie 78 (2017) 70–73

Annales d'Endocrinologie
Annals of Endocrinology

Letter to the Editor

Mucinous carcinoma of the thyroid: A case report and review of the literature

Carcinome mucineux de la thyroïde : à propos d'un cas et revue de la littérature

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Abstract

We report the case of a primary mucinous carcinoma of the thyroid in a man of 74 who had a 4-cm nodule in the right lobe of the thyroid, with a solido-cystic appearance on ultrasound associated with lymph node metastases. On scintigraphy, the nodule was hot and not extinctive. The patient underwent total thyroidectomy with a ipsilateral right lymph node dissection. The immunohistochemical study showed the negativity of CK 7 and CK 20 and the positivity of thyroglobulin and TTF 1. Postoperatively the rate of blood thyroglobulin 3 months after surgery had collapsed to 0.17 ng/ml. The evolution was marked by the appearance of pulmonary metastasis and the patient died 4 months after surgery. Histological study showed the presence of almas of neoplastic cells surrounded by large deposits of extracellular mucin. Primitive mucinous carcinoma of the thyroid is a rare tumor which differential diagnosis is established on the positive immunohistochemistry of thyroglobulin and TTF1 but negative for other markers.
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Keywords: Mucinous carcinoma; Thyroid cancer; Mucin; TTF1

Résumé

Nous rapportons le cas d'un carcinome mucineux primitif de la thyroïde chez un homme de 74 ans qui présentait un nodule de 4 cm au niveau du lobe droit de la thyroïde, avec un aspect solido-kystique à l'échographie associé à des métastases ganglionnaires. À la scintigraphie, le nodule était chaud et non extinctif. Le patient a bénéficié d'une thyroïdectomie totale avec un curage ganglionnaire homolatéral droit. L'étude immuno-histochimique montrait la négativité de la CK 7 et CK 20 et la positivité de la thyroglobuline et du TTF 1. En postopératoire, le taux de thyroglobuline sanguin 3 mois après la chirurgie était effondré à 0,17 ng/mL. L'évolution a été marquée par l'apparition de métastases pulmonaires et le décès du patient 4 mois après la chirurgie. L'étude anatomopathologique a montré la présence d'almas de cellules néoplasiques entourées par des dépôts larges de mucine en extracellulaire. Le carcinome mucineux primitif de la thyroïde est une tumeur rare dont le diagnostic différentiel est établi sur l'immunohistochimie positive de la thyroglobuline et de la TTF1 mais négative pour les autres marqueurs.
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Mots clés : Carcinome mucineux ; Cancer thyroïde ; Mucine ; TTF1

1. Introduction

The mucinous carcinoma of the thyroid was first described in 1976 by Diaz-Perez [1].

It is an extremely rare non-epithelial primary malignant tumor of the thyroid. Only seven cases have been reported in the literature [2], thus, the clinical and histological features have not been widely documented. Our patient was a 74-year-old man who was a chronic smoker (60 pack years). He had no history of neck radiation or familial thyroid disease. A year before admission, he perceived a mass growing on his neck with dysphonia.

The clinical examination revealed a hard and painless nodule of 4 centimeters in the right lobe of the thyroid, with ipsilateral

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http://dx.doi.org/10.1016/j.ando.2016.02.007
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cervical lymph nodes, without dyspneaor deterioration of general condition. By naso-endoscopy it was identified that the right vocal cord was atrophied and immobile in its anterior half. Biochemical tests, routine blood counts, and biochemical tests were normal and TSHus concentration was within the normal range at 2.12 μUI/ml (0.25–4 μUI/ml). The blood rate of the Prostate Specific Antigen (PSA) was normal (0.36 ng/l). Ultrasonography identified an increased size of the right lobe of the thyroid (measuring 25.8 × 50 × 38.7 mm), within it, a solid and cystic heterogeneous nodule, in contact with the sidewall of the trachea, measuring 35 × 25 mm. The vascularization was essentially peripheral. The nodule was rated TI-RADS 4a. The presence of bilateral infra-centimetric cervical lymph nodes, which preserved architecture, were noted. Thyroid scintigraphy showed high uptake of the radioiodine by the thyroid nodule, with a fairly significant hypertrophy of the thyroid (Fig. 1). The patient underwent a total thyroidectomy with right cervical lymph nodes resection with no postoperative complications. Macroscopically, the tumor was a white and solid mass. Microscopically, the parenchyma was massively occupied by a moderately differentiated carcinomatous proliferation, made of solid glandular and cellular cords with a pool of extracellular mucin (Fig. 2). The cells were large with eosinophilic cytoplasm. This proliferation invaded the pericapsular tissue and there were vascular invasions. The cervical lymph nodes were massively invaded by the

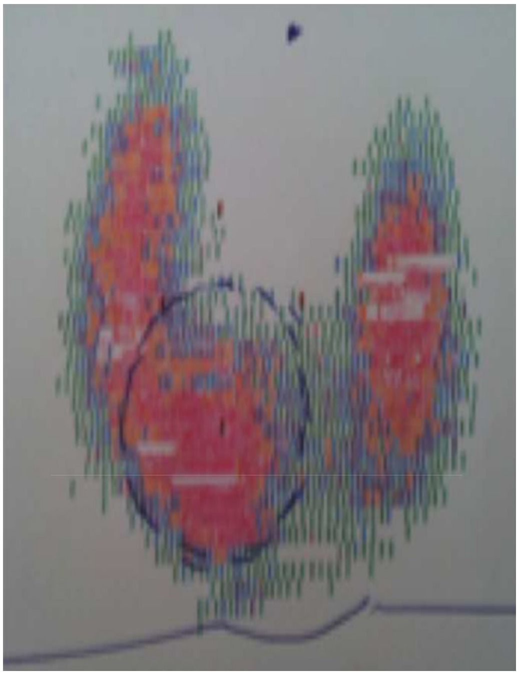

Fig. 1. Thyroid scintigraphy showing a high uptake of the radioiodine by the thyroid nodule.

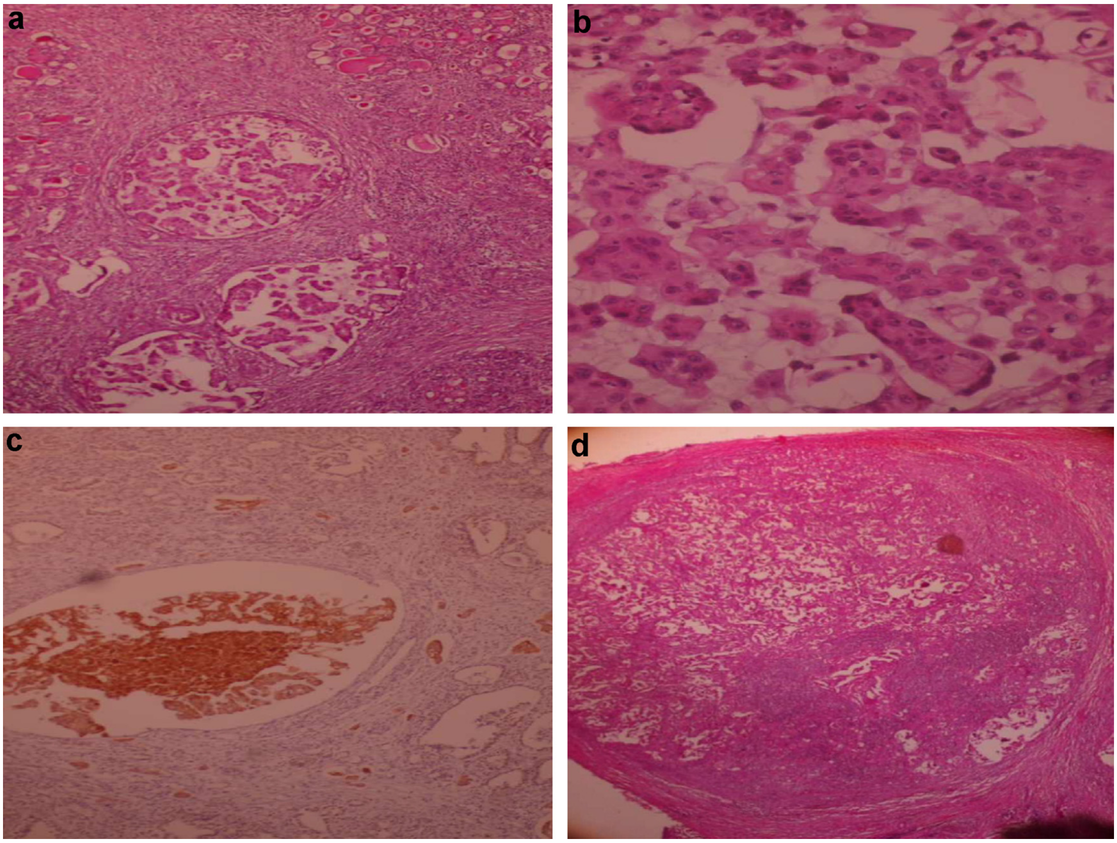

Fig. 2. a: thyroid parenchyma invaded by a carcinomatous proliferation with extracellular mucin. (Hematoxylin Eosin Staining); b: carcinomatous mass in a mucinous stroma; c: lymph node metastasis of a mucinous carcinoma of the thyroid; d: immuno-histochemistry: focal positivity to thyroglobulin.

Table 1
Reported cases of primitive mucinous carcinomas of the thyroid.

	Age/Gender	Tumor size (cm)	Treatement	Immuno-histo-chemistry	Metastases	Follow-up
Diaz-Perez et al. (1976) [1]	44/M	5.0 × 4.0 × 3.0	Partial thyroidectomy	NM	NM	NED, 8 years
Sobrinho-Simoes et al. (1985) [4]	40/M	2.8 × 2.5 × 1.5	Left lobectomy	Thy−	NM	NED, 15 mo
Sobrinho-Simoes et al. (1986) [5]	56/M	8 × 6 × 2	Total thyroidectomy Chemotherapy Radiotherapy	Thy+	N+ Lung+ Spine+	DOD, 2 years
Cruz et al. (1991) [6]	32/F	6 × 2.5 × 1.5	Total thyroidectomy Chemotherapy Radiotherapy	NM	N+ Lung+ Skin+	DOD, 8 mo
Tetsuo Kondo et al. (2005) [7]	82/F	3 × 2 × 2	Total thyroidectomy Radioisotope therapy	Thy+, TTF1+	N+ Skin+	DOD, 4 years
D'Antonio et al. (2007) [8]	59/F	NM	Total thyroidectomy + Lymph node dissection	Thy+, TTF1−/+	N+	DOD, 6 mo
Mnif et al. (2013) [2]	56/M	4 × 3 × 2 (left) 3 × 3 × 2 (right)	Total thyroidectomy	Thy+, TTF1+	N+	DOD, 1 mo
Present case (2014)	74/M	3.5 × 2.5	Total thyroidectomy + Lymph node dissection	Thy+, TTF1+	N+ Lung+	DOD, 4 mo

F: Female; M: Male; Thy: Thyroglobuline; N+ : Lymph Node; NED: no evidence of disease; DOD: dead of disease; NM: not mentioned.

same proliferation with a capsular break (49N+/57). Immunohistochemical study showed a positive immune-reactivity for thyroglobulin and thyroid-specific transcription factor 1 (TTF-1) and a negative immune-reactivity for CK7 and CK20, which supports the diagnosis of primitive mucinous carcinoma of the thyroid.

Chest, abdomen and pelvis CT found metastatic pulmonary micro-nodules. A radioiodine therapy was discussed, but the postoperative thyroglobulin rate of 0.17 ng/ml was discouraging.

The follow-up tests showed lung and supraclavicular lymph node metastases.

The patient died within 4 months after surgery from respiratory distress. Autopsy was not permitted.

2. Discussion

Primitive mucinous carcinoma of the thyroid is an extremely rare tumor. Only seven cases have been reported in the literature [2]. According to the World Health Organization classification system [3], this type of thyroid carcinoma is characterized by the presence of clusters of neoplastic cells surrounded by extra-cellular mucin deposition, and by positiveTTF1 and thyroglobulin, and negative calcitonin and CGRP.

The Table 1 summarizes the reported cases of primitive mucinous carcinomas of the thyroid. The time to diagnosis ranged from 2 months to 2 years. The most common clinical manifestation was a nodular goiter with cervical lymph nodes. One patient had dysphonia, and another patient had dysphagia. Only one patient received radioisotope therapy in which the tumor size was 3 cm. The thyroglobulin postoperative rate was not specified. In our case, the tumor expressed thyroglobulin and had some uptake at preoperative radio-iodine. However, although the patient was metastatic, the postoperative thyroglobulin level was very low. This might be explained by dedifferentiation of the lung metastases. Alternatively, this discrepancy can be explained by the presence of thyroglobulin antibodies. These can interfere with thyroglobulin assays, which, unfortunately was not tested [9]. Of the seven cases reported, five had nodal and lung metastases, with survival ranging from 1 month to 2 years. While the other two patients remained alive without significant recurrence during their follow-up [1,2,4–8]. In our case, the patient had supraclavicular lymph nodes and lung metastases and died 4 months after surgery.

Differential diagnosis must be discussed with other primary tumors of the thyroid expressing intracellular mucin, including papillary, medullary, mucoepidermoid carcinomas, and follicular adenomas [3,10]. In our patient, the diagnosis of medullary carcinoma of the thyroid was not retained because of the non-existence of criteria such as sheets, packets, or irregular islands traversed by delicate fibro vascular septa [11]. However, calcitonin was not initially measured.

Unusual follicular carcinoma is characterized by the presence of significant mucin [11]. However, histological study of the present tumordid not show any of the typical features of follicular tumors such as fibrous capsule or follicular architecture with variable amounts of colloid. Undifferentiated carcinomas sometimes have a mucin production [12]; however, the tumor cells in our case were not pleomorphic and mitotic activity was not high like conventional undifferentiated carcinomas.

Differential diagnosis should exclude metastatic carcinoma of the lung, breast, colon and other organs [3]. In our case, these diagnosis were ruled out at least for metastatic carcinoma by a nomal PSA value, a digestive endoscopy and normal pelvic CT.

The histogenesis of mucinous carcinoma of the thyroid is still controversial.

The ultimobranchial body, the solid cell nests that are embryonic remnants and the minor intrathyroid salivary glands are proposed as the origins of mucinous carcinoma [3]. Despite the lack of follicular structure and colloidal substance, focal thyroglobulin and TTF-1 expression led to suggest that the primary mucinous carcinoma is a poorly differentiated carcinoma derived from thyroid follicular cells [7].

Disclosure of interest

The authors declare that they have no competing interest.

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